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A CLINICAL AND PATHOLOGICAL STUDY OF THE HEART IN DIPHTHERIA

BY WILLIAM E. HUME AND S. J. CLEGG

With Plates 1 and 2

IN the summer of 1912, we commenced an investigation into the irregularities of the heart which occur in certain cases of diphtheria. From that time to the beginning of March, 1914, 573 cases of diphtheria were admitted to the City Hospital for Infectious Diseases, Newcastle-on-Tyne.

All these cases were under the daily supervision of one of us (S. J. C.), and when any irregularity of the heart and pulse was detected, polygraphic records were obtained. Other cases were similarly investigated if the general condition of the patient on admission suggested that the heart would be affected in a later stage of the disease, even though the rhythm of the heart was regular during the early stages. In this way we have obtained polygraphic records of seventy cases, of which thirty were found to be normal. Of the forty cases which presented irregularities, twenty-two showed the characteristics of a sinus arrhythmia and were associated with normal cardiac signs and symptoms.

The remaining eighteen cases presented many different types of heart irregularity and form the subject of this communication. Though the varieties of arrhythmia are great, the cases fall naturally into certain clinical groups. For instance, in Group I six cases are described which had many features in common: the patients were very ill from the onset of the disease, the hearts presented gross and varying irregularities of rhythm, and the pathological picture in four cases was identical.

In Group II nine cases are included which manifested a less serious clinical condition in the early stages than those in Group I; although the patients were seriously ill at some period of their rather prolonged stay in the hospital, there was less variety in the types of arrhythmia, and in two fatal cases the pathological lesions of the heart were slight as compared with the gross changes found in the four instances in Group I.

In Group III three mild cases are described in which some cardiac irregularity occurred without any other sign of involvement of the heart.

Group I.

In this group are included six cases which presented many features in common. On admission the patients were found to be suffering from a severe attack of diphtheria. The membrane in each case was extensive and luxuriant,

[Q. J. M., Oct., 1914.]

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and the general manifestations of a severe toxæmia were present. There was great prostration, vomiting occurred frequently, and death took place in each instance before the fifteenth day. Each case in this group was at once recognized as presenting certain general features which called for an early and constant study of the heart.

The important clinical features of each case are shown in Table I, in which the daily rate of the heart and the types of arrhythmia are set forth in detail. Three of these cases have already been described in considerable detail in *Heart*, vol. v, No. 1, p. 25, and it is only intended to refer to them in so far as they present points of similarity or contrast with the other three cases.

The similarity which was found in the clinical and pathological pictures of the cases already published was present also in the three later cases, and a summary of the three earlier forms an efficient introduction to the more detailed description of the three later cases.

Cases I, II, and III. All three children attended the same school and presumably contracted the disease from the same source. The duration of the illness, which terminated fatally in all three cases, was almost identical, as two of them died on the thirteenth day of illness and the third died on the fifteenth day of illness. The march of the disease from day to day gave rise to changes in the clinical picture which followed each other with such regularity that one description might have served for all three cases. The vomiting, pallor, gradual dilatation of the heart, the altered character of the heart-sounds, the types of arrhythmia, the subnormal temperature and the other manifestations of toxæmia were present in almost each particular in all three cases. This coincidence is particularly striking in the time of appearance of the various types of arrhythmia. Premature beats of the heart, which were proved to be of auricular origin in one case and probably also were so in the other two cases, appeared on the ninth day in two cases and in the third case on the seventh day. In two cases a nodal rhythm appeared on the tenth day and in the third case on the eighth day. A condition thought to be auricular flutter was noted in two of them, in one instance on the eleventh day and in the other on the twelfth day.

Though the general similarity between the first and the last three cases is great, the latter must be described in some detail in as far as the arrhythmia of the heart is concerned.

Case IV. Eva J., aged 7 years, was admitted to the hospital on the third day of illness, suffering from diphtheria. A swab had been taken and Klebs-Loeffler bacilli were found. 4,000 units of antitoxin were administered on admission, and next day a further dose of 6,000 units was given. The membrane extended over both tonsils, and there was bleeding from the throat and nose. The face was pale and anxious, and there was great prostration. On the fourth day purpuric spots appeared on the trunk and upper arms. Vomiting occurred early and the child died on the tenth day of illness. The apex beat of the heart was found to be in the nipple line on the fourth day, and the first sound of the heart heard at the apex was short and sharp. Polygraphic records, which were taken frequently between the third and the sixth days, revealed a normal rhythm. On the sixth day the curve shown in Fig. 1 was obtained.

The jugular tracing is occupied by single waves in each cardiac cycle, which appear quite regularly. The upstroke of the wave corresponds to the beginning of ventricular systole, and there is no evidence of an *a* wave preceding it.

It would seem probable that the auricles and ventricles are contracting simultaneously and that the focus of stimulation resides in the auriculo-ventricular node. The fourth peak in the jugular curve, however, is bifid, and the upstroke precedes the marking (4) by a greater interval than do the remainder of the upstrokes. In this cycle the auricular contraction slightly precedes the ventricular contraction and in this way the bifid top and the earlier appearance of the upstroke are accounted for. Tracings of this type were obtained throughout the sixth day. On the seventh day the rhythm of the heart changed, and the pulse was found to be completely irregular and Fig. 2 was obtained.

It is apparent that the radial pulse is completely irregular, that in the jugular curve there is a prominent wave at the beginning of systole *c*, and that

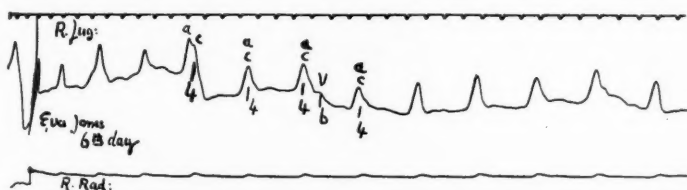


FIG. 1. Polygraphic curves from right jugular vein and right radial artery. In the jugular tracing there is a single large wave *ac*. In the fourth jugular cycle the wave is notched and the first peak is due to an auricular contraction. Rate = 100.

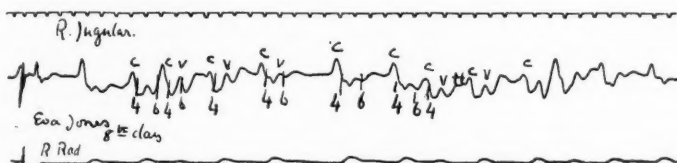


FIG. 2. Polygraphic curves from right jugular vein and right radial artery. Radial pulse is completely irregular. Ventricular form of venous pulse.

no wave *a* indicative of auricular contraction precedes *c*. It would seem certain that this curve indicates auricular fibrillation. The next day (the 8th) identically the same curves were obtained, and so also up to midday on the ninth day of illness.

Case V. John M., aged 4 years, was admitted on the sixth day of illness in an advanced state of toxæmia. 4,000 units of antitoxin had been administered on the third day of illness before admission to the hospital. There was an extensive membrane over both tonsils and the soft palate. The child was pale, and prostration was great. The temperature on admission was 99.4°, on the seventh day 99°, and on the eighth day fell to 98°; between the ninth and eleventh days (the day of death) the temperature ranged between 97° and 98°. The pulse rate was slow and perfectly regular throughout. It never dropped below 62 beats per minute, nor exceeded 70 beats per minute. Numerous tracings were obtained from the seventh to eleventh days, and Fig. 3 is representative of them.

The radial pulse was so small that it was impossible to obtain a record from it, and it was necessary to utilize the apical impulse as the index of the

commencement of ventricular systole. It is apparent that the beginning of the ventricular upstroke corresponds with the first upstroke in the jugular curve *c*. This is followed by a *v* wave. No wave indicative of auricular contraction precedes the wave marked *c*. The venous curve would appear to be open to three interpretations. In the first place the ventricular form of venous pulse and the regularity of the ventricles would point to the presence of auricular fibrillation and heart-block. A similar tracing with this interpretation has been published by Price and Ivy Mackenzie. In the second place the auricles may have been in a state of 'flutter' and the auricular contractions may have been too small to make any impression on the venous pulse. In the third place the auricles may be contracting at the same rate as the ventricles, but do so either simultaneously or later than the ventricles. The comparatively slow rate of the

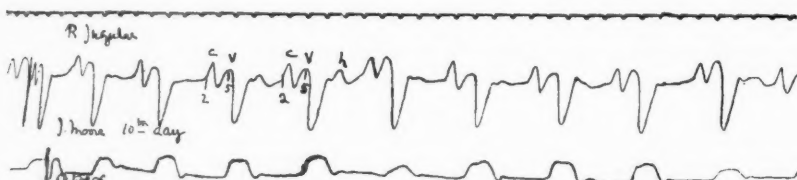


FIG. 3. Polygraphic curves from right jugular vein and apex beat. Ventricular systolic rise (*c*) in jugular curve, followed by (*v*) wave. Rate = 66.

ventricles and the form of the jugular curve make it probable that the first is the correct interpretation. The rhythm in the following case was practically identical with the foregoing, and the same explanation probably holds in both cases.

Case VI. Violet T., aged 6 years, was admitted on the sixth day of illness and died on the eighth day. 2,000 units of antitoxin had been given on the fifth day and on admission 4,000 units were injected. The child was extremely ill, pale, prostrate and vomiting. The temperature was 97° and the pulse rate was 72. On the seventh day the following polygraphic tracing was obtained (Fig. 4).

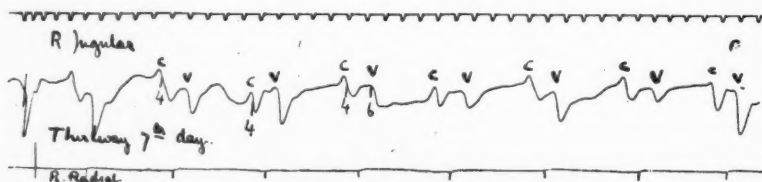


FIG. 4. Polygraphic curves from right jugular vein and right radial artery. Ventricular form of venous pulse. Rate = 60.

The similarity of this curve to Tracing 3 is very great and the pulse rate is slightly slower—60 beats per minute. Of the alternative explanations the most probable would appear to be that there is fibrillation of the auricles together with complete auriculo-ventricular dissociation. The ventricular rate is faster in these instances of heart-block than it is in chronic heart-block in adults. Even in adults the idioventricular rate may reach 60 beats per minute,

and there may be in children an idioventricular rate which naturally exceeds that of the adult.

Attention has already been called to the similarity which all the cases forming this group bear to each other. The infection was virulent, and in no case was antitoxin administered before the third day. There were features in the general appearance of the patients and in the local condition of the throat which justified a bad prognosis. Such features were the extreme pallor and prostration and the extent and character of the membrane, together with the frequent occurrence of bleeding from the throat and nose. Dilatation of the heart was always obvious before the sixth day and the tension in the radial arteries was very low. As a result of the frequent investigation of these six cases by the polygraph a great variety of heart irregularities has been collected. Premature contractions arising in the auricles or ventricles usually heralded the occurrence of some grosser type of arrhythmia. It will have been apparent that not only did each case present a particular arrhythmia, but that the rhythm of the heart frequently changed from day to day. This fact, which was emphasized in a previous publication, was corroborated in the three cases now published.

Pathological.

Autopsies were obtained in four of the six cases of this group, and the following is a brief account of the pathological findings. The hearts were removed on the day of death and were fixed in 10 per cent. formalin. After fixation the following pieces were removed for histological examination:

(1) Piece of auricular muscle—stained with (a) Sudan III and iron haematoxylin, and (b) iron haematoxylin and van Gieson's stain.

(2) Pieces of ventricular muscle—stained similarly to (1).

(3) A block of tissue from the junction of the superior vena cava and the right auricular appendix, including the sino-auricular node—stained with haematoxylin and van Gieson's stain.

(4) A block of tissue including the auriculo-ventricular node and bundle of His—stained with haematoxylin and van Gieson's stain.

1. *The auricular muscle.* The auricular muscle stained with Sudan III and haematoxylin always contained some excess of fat, though never comparable to the amount found in the ventricular muscle. There was usually an increased vascularity to be detected amongst the auricular muscle fibres, and occasionally small haemorrhages were seen.

2. *The ventricular muscle.* In all four instances the ventricular muscle contained a very large quantity of fat. It was found diffusely throughout the muscle of both ventricles, and nearly every muscle fibre contained some fat. In some fibres it occurred as fine granules and in others as large round droplets. Some fibres obviously were more affected than others. In the cases of J. H. and E. J. there were marked patches of interstitial myocarditis, and in all cases the smallest capillaries were dilated and engorged with blood.

3. *The sino-auricular node.* Throughout each node there was a considerable increase of vascularity and actual haemorrhages were fairly common. It is thought also that there was an increased infiltration with cells of the lymphocytic class.

4. *The auriculo-ventricular node and bundle of His.* Though the *a-v* node invariably showed dilated and engorged capillaries no gross histological changes could be discovered in them; and likewise there was no abnormality in the histological appearances of the auriculo-ventricular bundle or of its two main branches. Certainly there was a greater degree of vascularity in the *a-v* bundle of J. L. than in the other three cases, and it was in this case that a period of 2:1 heart-block was detected. The relationship between the pathological picture and the types of arrhythmia will be discussed after a description of the clinical appearances of the other cases and the histological findings in the hearts of two of them.

Group II.

In this group the toxæmia was marked in all the cases and there was a copious septic membrane in the throat. Two of the cases died, on the forty-second and forty-sixth days respectively. The remainder were seriously ill for long periods, and their stay in the hospital was prolonged (114–131 days).

Robert S., aged $5\frac{1}{2}$ years, was admitted on the fourth day of disease, and 4,000 units of antitoxin were injected on admission. The pulse-rate on admission was 124, but afterwards till the twenty-third day it did not exceed 84. From the twenty-third day to the fortieth day, on which the child died, the pulse-rate varied between 84 and 118. Physical examination of the heart indicated that it was the seat of pathological changes, as on the 10th day there was a weakening of the first sound and displacement of the apex beat outwards.

Numerous and varying irregularities of the heart were discovered between the eighteenth and forty-sixth days, and the following table shows succinctly the varieties of arrhythmia and the days on which they were detected:—

18th day	Auricular extra-systoles.
							Ventricular „
							Reversal of the normal beat.
19th day	Auricular extra-systoles.
							Ventricular „
							Reversal of the normal beat.
20th day	Ventricular extra-systoles.
29th–46th day	Ventricular extra-systoles.

From the eighteenth day to the twentieth day auricular extra-systoles were frequent, and Fig. 5 is characteristic of their appearance. The fifth cycle is premature, and the proof that the prematurity is due to the early appearance of an auricular contraction is to be found in a study of the jugular tracing.

Ventricular extra-systoles were very frequent from the eighteenth day onwards, and Fig. 6 is typical of the condition.

In this figure the fourth cycle from the ordinate is a premature beat, and a study of the jugular tracing shows that it is due to a premature contraction of the ventricles. The auricular rhythm is undisturbed, and the post-extrasystolic pause is fully compensatory. Occasionally ventricular and auricular extra-systoles occurred in close relationship to each other. In Fig. 7 the fourth cycle to the right of the ordinate is due to a premature contraction of the ventricle.

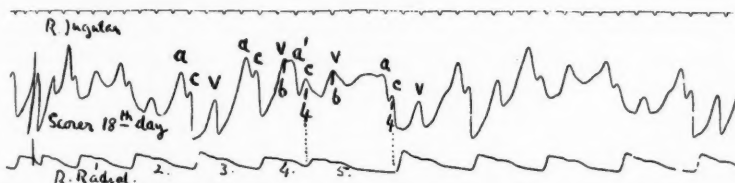


FIG. 5. The marking 6 of the fourth cycle occurs on the first apex of a broad wave. This is immediately followed by a second apex which is the *a* wave of the premature beat.

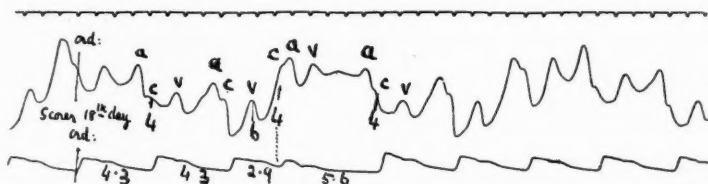


FIG. 6. Polygraphic curves from right jugular vein and right radial artery. The fourth cycle is premature, and measurement shows that the ventricle (*c*) has contracted prematurely. The *c* wave is followed by the physiological auricular contraction, and together they give rise to a large wave *ca*.

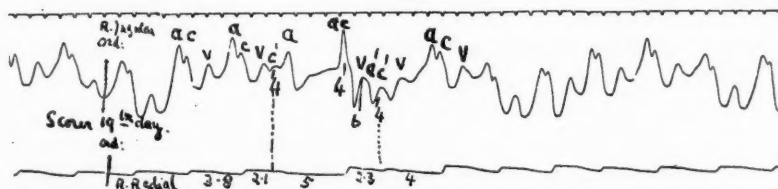


FIG. 7. The fourth cycle is premature and is due to a premature contraction of the ventricle (*c*¹). In the next cycle auricles and ventricles contract together (*ac*), followed in the sixth cycle by an auricular extra-systole.

The fifth ventricular contraction is also slightly premature and the simultaneous contraction of auricles and ventricles gives rise to a single large wave *ac*.

The sixth cycle is likewise premature and is due to a premature contraction of the auricles. The ventricular post-extrasystolic pause is almost fully compensatory, whereas the auricular post-extrasystolic pause falls considerably short of it.

Reversal of the cardiac beat. In Fig. 8 a very exceptional mechanism is presented. The apparent *v* wave of the fifth cardiac cycle is exceptionally large,

and it is thought that a premature contraction of the auricle is included in it which meets with no response from the ventricle. The sixth cycle commences with a small wave *c*, which is followed by a large wave occurring *during* ventricular systole. That this is due to a contracting auricle seems almost certain from a consideration of the position of the marking 6, which falls considerably after it. The seventh cycle is composed of a simultaneous contraction of auricles and ventricles. Thereafter the normal rhythm is re-established. It is noteworthy that the rate of the ventricles is considerably slowed during the period of most marked irregularity. This fact is accounted for by the pause which the ventricles make before they initiate their own contraction, having been disappointed of an auricular impulse from above.

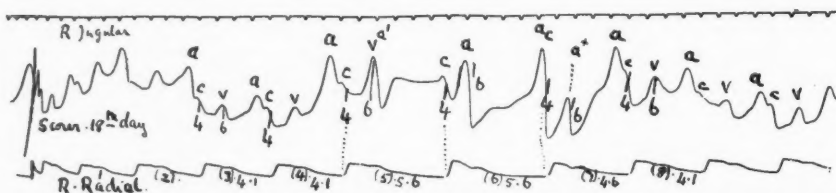


FIG. 8. The *v* wave of the fifth cycle is so prominent that it is thought to include an *a* wave. The sixth cycle is delayed and auricular follows ventricular contraction, while the seventh is a nodal beat.

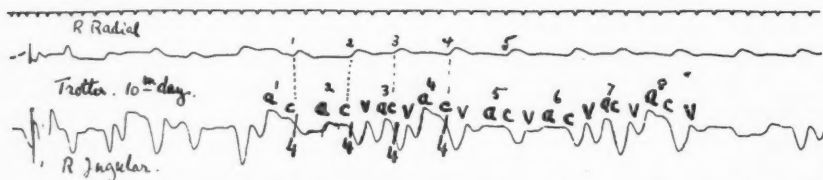


FIG. 9. Lower curve is from the right jugular vein and the upper from the right radial artery. Of the cycles which are labelled, the first two are normal *acv* sequences, the third contains a premature contraction of the ventricle, while in the fourth the auricular contraction is premature.

Premature beats of the ventricles persisted for some weeks, although the heart became regular before the child died on the forty-second day.

The second fatal case of this group, Margaret T., aged 5 years, was admitted on the second day of illness with an extensive membrane on both tonsils, and a purulent discharge from the nose. The pulse-rate on admission was 120 and remained rapid, varying between 90 and 144, until the forty-second day, on which the child died. The pulse was perfectly regular until the ninth day. On the ninth and tenth days the pulse had the character depicted in Fig. 9, and the following are its characteristics:

Though the rhythm is for the most part regular, premature beats are to be seen in the radial tracing. These correspond to single waves a^3c in the jugular curve, measurement of which shows that the ventricular wave *c* is alone premature, while the auricular wave a^3 falls at the normal physiological moment. The premature beats are due to premature contractions of the

ventricles, but do not interfere with the physiological rhythm. The following contraction a^4 , however, is premature and in the next four cycles the same sequence of events is repeated. This type of arrhythmia was almost constantly present until the patient died on the forty-ninth day.

Both clinically and pathologically the two cases which have just been described differed considerably from all the cases included in Group I. Both R. S. and M. T. were in a clinical condition in the early stage very similar to that which will be described in the other cases of this group. Arrhythmia of the heart was the first indication that the heart was pathologically involved in both cases, and though various forms of arrhythmia appeared and disappeared, it was not surmised that a fatal termination would ensue. In both cases there was a sudden increase in the pulse-rate about the fortieth day, and in the case of M. T. pharyngeal paralysis appeared on the thirty-sixth day, and paralysis of the diaphragm on the forty-first day, and in the case of R. S. diaphragmatic paralysis was noticed on the forty-fifth day. Both children died on the day following the appearance of the diaphragmatic paralysis.

A post-mortem examination was only obtained in the case of M. T., and the histological appearances of this heart differed very materially from the four examples which were obtained in Group I. The heart of M. T. was investigated in exactly the same manner as were the hearts in Group I. The increase of fat, which was such a noteworthy feature in the fatal cases of Group I, was completely absent in this case. Beyond some increase of vascularity throughout the whole heart, the only pathological feature that was discovered was some scattered patches of interstitial myocarditis in the ventricular muscle.

The other cases of this group were seriously ill for a considerable time, and three of them (A. S., G. R., and V. L.) had many features in common.

On admission they were all considered serious cases and showed signs of a grave toxæmia. The rate of the heart remained rapid throughout their stay in the hospital, and in one case (A. S.) the pulse-rate was 100 on discharge. In each case there were the ordinary physical signs associated with dilatation of the heart, namely, displacement of the apex beat, weakening of the first sound, and a systolic murmur at the apex.

The first case, A. S., has been reported in the paper to which reference has already been made, though the chief facts may be here repeated. A. S., aged 6 years, was admitted in a very toxic condition, and on the fourth day the first sound of the heart was feeble and the apex was found in the nipple line. On the twentieth day a mitral systolic murmur was heard at the apex. The rate of the heart was always rapid, and even on discharge was 100 beats per minute. The rhythm of the heart was regular until the fifteenth day, when premature beats were detected. These were observed up to the forty-first day, when the child had an attack of paroxysmal tachycardia. On this and subsequent days the patient was very collapsed and vomited frequently. She appeared almost moribund and lay in a prostrate condition until the fifty-first day, when the events of the forty-first day were repeated in almost every detail. On both these days there were short and long attacks of paroxysmal tachycardia, and one of the attacks is shown in Fig. 10.

Each cardiac cycle during the paroxysm consists of two waves in the jugular

tracing, *ac* and *v*. From a comparison of this tracing with others in which electro-cardiographic records have been made it seems most probable that the exciting focus was in the auriculo-ventricular node. With this interpretation the first wave *ac* represents the simultaneous contraction of auricles and ventricles. After the second paroxysm the child lay for three days in a state of great collapse, but gradually recovered, though the pulse-rate was still 100 when she was discharged.

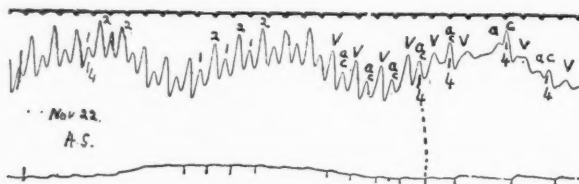


FIG. 10. Right jugular and right radial curves. The child moved her hand and this has deformed the radial curve. During the paroxysm there are two waves in each cycle (*ac* and *v*). The paroxysm ends abruptly, and there is a post-paroxysmal pause before the normal rhythm is resumed.

Gladys R., aged 7 years, was admitted on the second day of disease, and 6,000 units of antitoxin were administered on admission and a further dose of 6,000 units was given on the third day. The throat was covered with a thick membrane and the signs of a severe toxæmia were apparent; the child was prostrate and pale. The pulse-rate on admission was 130 and remained fast until the 120th day of disease, when it fell to 96 and the patient was discharged on the 124th day with a pulse-rate of 84.

During the first week the temperature ranged between 97° and 100° and was then normal for six weeks. On the fiftieth and fifty-first days the temperature rose to 99.8°–100.4°, and the pulse-rate quickened to 144 beats per minute.

The heart was early dilated, though the rhythm remained normal until the twenty-seventh day, when ventricular extra-systoles were recorded.

This arrhythmia persisted only for a short period, and the rhythm was regular until the child was discharged on the 124th day with a pulse-rate of 84. Her prolonged stay in the hospital was due to the fact that she developed paralysis of the diaphragm on the forty-fifth day.

Violet L., aged 9 years, was admitted on the third day of illness, and both on that day and the day following 4,000 units of antitoxin were injected. The child had a toxic appearance and the tonsils were covered with membrane. The membrane separated on the sixteenth day, but fresh membrane appeared on the seventeenth day, a large piece of which came away on the same afternoon. There were evidences of cardiac dilatation from the sixteenth to the seventy-fourth days, and nasal phonation was detected on the eleventh day.

The pulse-rate on admission was 128 and fell to 86 on the seventh day. The speed of the heart varied considerably throughout, and the temperament of the child may have been more responsible for this variation than any changing condition of the heart itself. The temperature on admission was 102° and at the end of a week had fallen to 98.4°. Except for a rise of temperature to 99° on the fifty-first day the range remained constantly between 97° and 98.4°.

The rhythm of the heart remained perfectly regular until the sixty-first day, when ventricular extra-systoles were recorded. These were infrequent and only persisted for a few days. No other cardiac irregularity was detected. The child was discharged on the 114th day with a pulse-rate of 80.

The remaining cases of this group were less severe than the foregoing and in no stage of their illness did they give rise to anxiety as to the ultimate issue.

Norman C., aged 13 years, was admitted on the fourth day of illness and was injected with 6,000 units of antitoxin on the day of admission. A further dose of 4,000 units was injected the next day. On the right tonsil there was a thick, grey, white membrane which extended on to the soft palate. The submaxillary glands on the right side were considerably enlarged. The face was flushed, but there were no evidences of toxæmia such as the condition of the throat would have suggested.

The temperature on admission was 98.4° . On the seventeenth and eighteenth days the temperature rose to 99.6° and 101° respectively, and thereafter the range was normal. The pulse-rate on admission was 84. During the days on which there was a rise of temperature the pulse correspondingly increased in rate, but on other occasions it varied between 70 and 90 beats per minute. On the fifteenth day nasal phonation was detected. There was ciliary paralysis on the forty-eighth day. Up to the sixteenth day the heart remained regular. From the sixteenth to the thirty-first days ventricular extra-systoles were recorded, and Fig. 11 is an example.

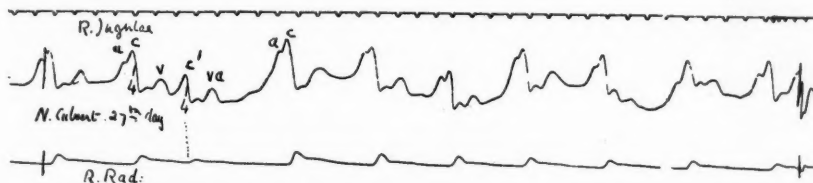


FIG. 11. Polygraphic curves from right jugular vein and right radial artery. The third cycle is premature and corresponds to c' , a premature contraction of the ventricle. Physiological a falls with the v of the premature beat.

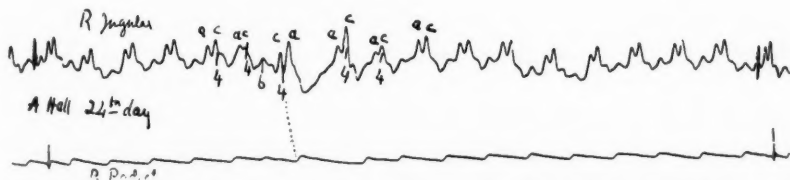


FIG. 12. Right jugular and right radial curves. The sixth cycle is premature and the prematurity involves both a and c ; this is a nodal extra-systole. The seventh cycle is a ventricular extra-systole.

After the thirty-fifth day the heart became regular and remained so until the child was discharged on the seventieth day.

Annie H., aged 9, was admitted on the sixth day of illness with membrane on the right tonsil and the right side of the uvula. 4,000 units of antitoxin were administered on the day of admission. The general condition was good and the membrane early separated. From the sixth day onwards a slight weakening of the first sound of the heart was detected. The pulse-rate on admission was 100, and on the eighth day it had fallen to 88. From the ninth day to the seventy-seventh day the rate never exceeded 88 beats per minute. Beyond a rise of temperature to 100.2° on the seventh day the range was normal. Nasal phonation was detected on the second day. From the twenty-fourth to the sixtieth day ventricular extra-systoles were recorded. In Fig. 12 the sixth and seventh cardiac cycles are premature.

In the sixth cycle the auricles and ventricles have contracted prematurely and there is a considerable shortening of the *a-c* interval. The stimulus for this almost simultaneous contraction of auricles and ventricles has probably arisen in the *a-v* junctional tissues. In the seventh cycle the ventricular precedes the auricular contraction by a considerable interval, and is followed by a compensatory pause. This is due to a premature contraction in the ventricles.

The child was discharged on the seventy-seventh day with a pulse-rate of 88.

Charlotte M., aged 10 years, was admitted on the eighth day of illness and had received 2,000 units of antitoxin on the fifth day of illness. On admission a further dose of 4,000 units was injected. On the eighth day the child was pale and had a toxic appearance. Patches of membrane persisted on both tonsils. On the seventeenth day of illness it was noticed that the first sound of the heart had the short abrupt character of a second sound, and on the eighteenth day the pulse was found to be irregular. Polygraphic tracings taken on this day are represented by Fig. 13.

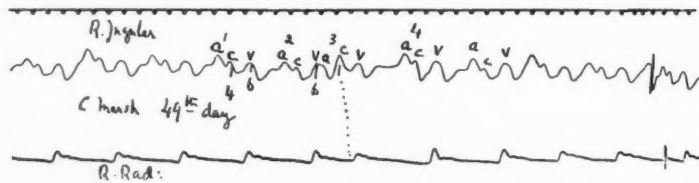


FIG. 13. Polygraphic curves from right jugular vein and right radial artery. The third cycle is premature and is due to a premature contraction of the auricles. a^3 falls on the *v* of the previous cycle and makes that wave broad.

In this figure a^3 is premature and deforms the *v* wave of the preceding cycle, making a much broader wave than the other *v* waves. The compensatory pause is not complete. Nasal phonation was detected on the twenty-ninth day of illness and ciliary paralysis on the thirty-first day of illness. Throughout the ninety-two days while the child was in the hospital the pulse remained comparatively slow and the range was constantly between 68 and 99. The temperature was normal throughout. The patient was discharged on the ninety-second day with a pulse-rate of 84.

Group III.

There remain to be described three cases which showed many points of similarity in that the cases were not admitted to the hospital before the fifth day of illness, and had not received antitoxin before the day of admission. There was no evidence of toxæmia, and the throat condition was not severe. Certain irregularities of the heart occurred in all of them, but the heart did not reveal any abnormality by the ordinary methods of examination.

Mary R., aged $2\frac{1}{2}$ years, was in the hospital for twenty-three days. On admission the pulse-rate was 80 and on the eleventh day it reached 96. For ten days the pulse remained quick. On the ninth day it was noticed that the pulse was irregular. The irregularity was due to premature contractions of the

ventricles, and this arrhythmia was present from the ninth to the fourteenth day. When the child was discharged from the hospital the pulse was perfectly regular at 80 to the minute.

In the case of Harry L., aged 15, premature beats of the auricles and ventricles were recorded between the twentieth and twenty-sixth days. He was admitted on the seventh day of illness, and again there was no evidence of toxæmia. The throat was congested, but there was no membrane on either tonsil. The pulse-rate was never fast and was not counted at more than 98 beats per minute. The ordinary examination of the heart did not reveal any abnormality.

In Fig. 14 it will be seen that the eighth cardiac cycle is premature, and from a consideration of the jugular curve it is evident that the prematurity is due to an auricular extra-systole.

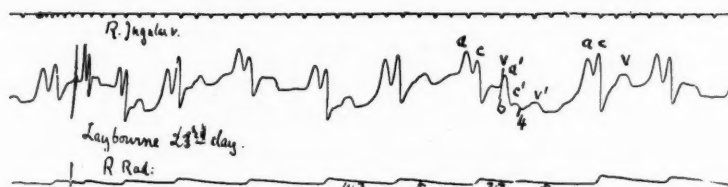


FIG. 14. Curves from right jugular vein and right radial artery. The eighth cycle is premature, and this is due to a premature contraction of the auricles.

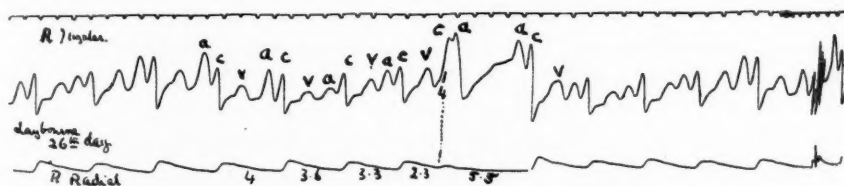


FIG. 15. Curves from right jugular vein and right radial artery. The eighth cycle is premature, and a ventricular extra-systole is evident.

The compensatory pause is not complete. Between the twentieth and twenty-sixth days ventricular extra-systoles were common, and an example is to be seen in Fig. 15.

In this figure the eighth cycle is premature, and by a consideration of the jugular curve the prematurity is found to be due to a premature contraction of the ventricle. The auricular rhythm is not disturbed and the compensatory pause is more than complete, the cycle previous to the premature beat and the premature beat itself measuring 7.8 fifths of seconds, while no other two normal cycles measure more than 7.6 fifths of seconds. During the last fortnight there was no irregularity of the pulse at all, and the boy was discharged cured.

The last case of the series, George C., aged 17, was admitted with small patches of membrane on the left tonsil and his general condition was good. He was in the hospital for twenty-four days, and on the fifteenth day ventricular

extra-systoles were recorded (Fig. 16). The pulse is slow, and at the sixth cycle a premature c^1 has deformed the v wave of the fifth cycle. The sixth auricular contraction, a^6 , is plainly seen as an isolated wave, and there has been no ventricular response. The seventh auricular contraction is premature.

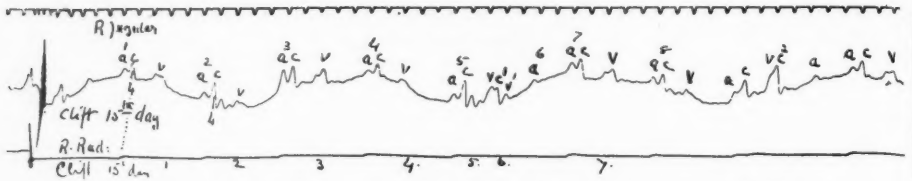


FIG. 16. Jugular and radial curves. The sixth cycle, c^1v^1 , is premature and is due to a ventricular extra-systole. The physiological (a^6) is seen as an isolated wave.

Summary.

At the commencement of this investigation it was not anticipated that a systematic polygraphic study in cases of diphtheria would reveal such a variety of irregularities of the heart, and the accompanying table, Table II, shows the types of arrhythmia which have been recorded in the cases which are now described (15) and in those whose detailed description appeared elsewhere (3).

Although the pathological changes in four cases of Group I were very marked, it is impossible to correlate the pathological lesions with the individual instances of arrhythmia of the heart. Irritative and destructive processes are taking place simultaneously and result in excitation or depression of the various functions of the heart muscle. For instance, it is impossible to state whether a nodal rhythm depends on hyper-irritability of the $a-v$ node, or a depression of the $s-a$ node allowing the lower node to usurp the function of pacemaker of the heart, which belongs properly to the upper node. Further, we have shown that the types of arrhythmia in each individual case may vary from day to day, a variation which is in all probability dependent upon varying and progressive pathological changes in the heart muscle and its nerves. It may be asserted, however, that any form of arrhythmia of the heart (except sinus arrhythmia) in diphtheria indicates that the heart muscle or nerves are involved in a pathological process, however mild the illness may otherwise appear to be, and that special precautions are necessary to keep the patient recumbent.

(The pathological preparations were made in the Pathological Department of the Durham University College of Medicine.)

A STUDY OF THE HEART IN DIPHTHERIA

15

TABLE I.

Group I.

Day of illness on admission.	Antitoxin.	General condition.	Throat.	Pulse.	Temperature.	Heart Examination.	Paralysis.	Polygraphic Curves.
	Day.		Day.		°			Day.
E. P. 3rd 5 years	3rd = 6,000	Toxic	Septic membrane right tonsil, uvula and palate. Enlarged glands	3rd = 110 4th = 120 5th = 68-104 9th = 88-116 10th = 100 11th = 99-4 12th = 128 13th = 100	3rd = 99-8 5 to 9 = 97 9th = 99-6 10th = 100 11th = 99-4 12th = 97 13th = 100	7th day. Apex nipple line. 1st sound muffled		3 & 5 = Normal 7th = Extra-systoles 8 & 10 = Auricular fibrillation and heart-block (Fig. 14) ¹ 11th = Auricular flutter (Fig. 15) ¹
J. H. 4th 7	4th = 6,000 5th = 4,000 8th = 6,000	Toxic	Thick membrane both tonsils	4th = 122 5 to 6 = 102-106 8th = 92 9 to 12 = 90-100 13th = 116 14th = 122	4 and 5 = 100 6th = 99 7th = 97-6 8 and 9 = 99 10 to 12 = 97-98 12 to 15 = 97-98-4	4th day. Normal 5th day. Apex nipple line. Weak 1st sound; reduplicated 2nd	10th day. Nasal phonation	5 & 8 = Normal 9th = Auricular extra-systoles (Fig. 1) 10 & 11 = Nodal rhythm (Figs. 2-8) ¹ 12th = Auricular flutter (Fig. 9) ¹ 13th = Auricular extra-systoles
F. L. 6th 7	5th = 8,000	Toxic	Membrane both tonsils. Epistaxis. Nasal discharge	6th = 90 8th = 100 9th = 94 10th = 74-78 11th = 84-92 12th = 99-114 13th = 112 14th = 80-112 15th = 72	6th = 98 8th = 97 9 to 11 = 98-4 12 to 15 = 97	7th day. Heart sounds and position normal 8th day. Apex displaced out. Short 1st sound		Normal to 8th day 9th = Extra-systole (Fig. 8) ¹ 10th = Nodal rhythm (Fig. 12) 12th = Heart-block (Fig. 13) Regular till 6th day 6th = Nodal rhythm 7th = Auricular fibrillation 8th = " "
E. J. 3rd 7	3rd = 4,000 4th = 6,000	Toxic	Both tonsils, palate. Bleeding from throat and nose	3rd = 112 4th = 80-112 6th = 72 7th = 84-100 8th = 82 9th = 104-114	3rd = 99-4 3 to 9 days subnormal	4th day. Dilatation	Nasal phonation	
J. M. 6th 4	3rd = 4,000	Pallor Toxic	Membrane	6th = 90 7th = 70 8th = 68 9th = 66 10th = 62 11th = 68	6th = 99-4 7th = 99 8th = 98 9 to 11 = 97-98	9th day. Dilatation	10th day. Nasal phonation	10th = Auricular fibrillation and heart-block
V. T. 6th 6	5th = 2,000 6th = 4,000	Toxic	Thick membrane left tonsil and pillars of fauces. Nose bleeding	6th = 72 7th = 56	6th = 97 8th = 97	Dilatation		7th = Auricular fibrillation with heart-block

¹ Heart, vol. v, No. 1, 1913.

Group II.

Day of illness on admission.	Antitoxin.	General condition.	Throat.	Pulse.	Temperature.	Heart Examination.	Paralysis.	Polygraphic Curves.
R. S. 4th 5½ years	Day. 4th = 4,000	Toxic	Laryngeal	Day. 4th = 124 6 to 45 = 84-106 46th = 118	Day. 4 to 46 = 97-99	45th day. Dilatation	22nd day. Nasal phonation	Day. 4 to 18 = Regular 18 and 19 = Auricular extra-systoles and reversal of beat 20th = Ventricular extra-systoles
M. T. 5	2nd = 4,000 4th = 4,500	12 to 36, Improved. 36th, Pale and vomiting. 41st. Very ill	Membrane left tonsil. Nasal discharge	2nd = 120 5 to 38 = 80-116 40th = 144 41st = 132 42nd = 124	2nd = 101-6 3 to 13 = 97-98-4 14 to 41 = Subnormal 42nd = 100-2	9th day. Dilatation	36th day. Nasal phonation. Diaphragmatic paralysis 41st day	Till 9th = Regular 9 and 10 = Extra-systoles 11th = Auricular fibrillation and heart-block 12th = Extra-systoles 13 to 36 = Regular 41st = Irregular
A. S. 6	3rd = 4,000 6th = 4,000	Toxic	Patching of both tonsils. Enlarged submaxillary glands	3rd = 144 4th = 120 7 to 40 = 84-110 41st = 120 51st = 128 52 to 126 = 88-128 131st = 100	3rd = 99-6 4 to 52 = 96-98 54th = 99-4 55 to 101 = 97-98 102nd = 99-2 103 to 131 = 98	4th day. Dilatation	Diaphragmatic paralysis 51st day	Till 15th = Regular 16th = Premature beats 41st = Paroxysmal tachycardia 51st = Ditto
G. R. 7	2nd = 6,000 4th = 6,000	Toxic. Previous history of a weak heart	Thick membrane both tonsils and palate. Glands enlarged	2nd = 130 5th = 132 6 to 49 = 108-116 50 to 51 = 99-8-100-4 51 to 123 = 108-120	1 to 8 = 97-100 8 to 49 = Normal 50 to 51 = 99-8-100-4 52nd day. Normal, and subsequently	Early and persistent dilatation	Nasal phonation. Diaphragmatic paralysis 45th day	Till 27th = Normal After 27th = Extra-systoles
V. L. 9	3rd = 4,000 4th = 4,000	Toxic	Membrane both tonsils, which separated on 5th day. Fresh membrane both tonsils 6th day	3rd = 128 4th = 70-120 5th = 54 6 to 45 = 70-112 45 to 51 = 80-90 52 to 114 = 97-98-4	3rd = 102 4th = 100 5th = 99 6 to 45 = 97-98-4 45 to 51 = 97-99 52 to 114 = 97-98-4	16th to 74th day. Cardiac dilatation	Nasal phonation from 11th day	Extra-systoles
C. M. 10	5th = 2,000 8th = 4,000	Toxic	Remains of membrane on both tonsils	8th = 96 9 to 92 = 68-90	8 to 92 = 96-5-98-4	17th day. Dilatation	29th day. Nasal phonation	After 18th = Auricular and ventricular extra-systoles throughout

Group II (continued).

Group II (continued).

Day of illness on admission.	Antitoxin.	General condition.	Throat.	Pulse.	Temperature.	Heart Examination.	Paralysis.	Polygraphic Curves.
Day.				Day.	Day.			
A. H. 6th 9 years	6th = 4,000	Good	Membrane on right tonsil and right side of uvula	6th = 100 7th = 98 8th = 88-98 9 to 77	6th = 98-6 7th = 100-2 8 to 77 = 97-98	6th to 62nd day. Slight weakening of 1st sound	2nd day. Nasal phonation.	24th to 60th day. Ventricular and nodal extra-systoles
N. C. 4th 13	4th = 6,000 5th = 4,000	Fair	Right tonsil enlarged. Membrane extending to soft palate. Glands enlarged	4th = 84 6th = 94 8th = 68 10th = 56 11 to 70	4th = 98-4 5 to 16 = 97-98 17th = 99-6 18th = 101 20 to 70 = 97-99	15th day. Nasal phonation 48th day. Ciliary paralysis	16th to 35th day. Ventricular extra-systoles 70th day. Normal	

Group III.

Day of illness on admission.	Antitoxin.	General condition.	Throat.	Pulse.	Temperature.	Heart Examination.	Paralysis.	Polygraphic Curves.
Day.				Day.	Day.			
M. R. 5th 2½	5th = 2,000	Good	Patches on both tonsils	5th = 80 11th = 96 13th = 108 15th = 112 21st = 96 24th = 76 25th = 82	97-98 throughout	13th day. Dilatation		9th to 24th day. Ventricular extra-systoles
H. L. 7th 15	7th = 2,000	Good	No membrane. Congested throat.	7th = 64 7 to 26 = 60-74 27 to 42 = 72-100	7 to 28 = 97-98 28 to 30 = 98-98-4 31 to 42 = 97-98	Normal throughout		20th to 26th day. Ventricular and auricular extra-systoles
G. C. 4th 17	3rd = 4,000	Fair	Small patches on left tonsil	64-68	97-97-5	Normal		Ventricular extra-systoles
E. Y.	—	—	—	—	—	—		Ventricular extra-systoles

TABLE II

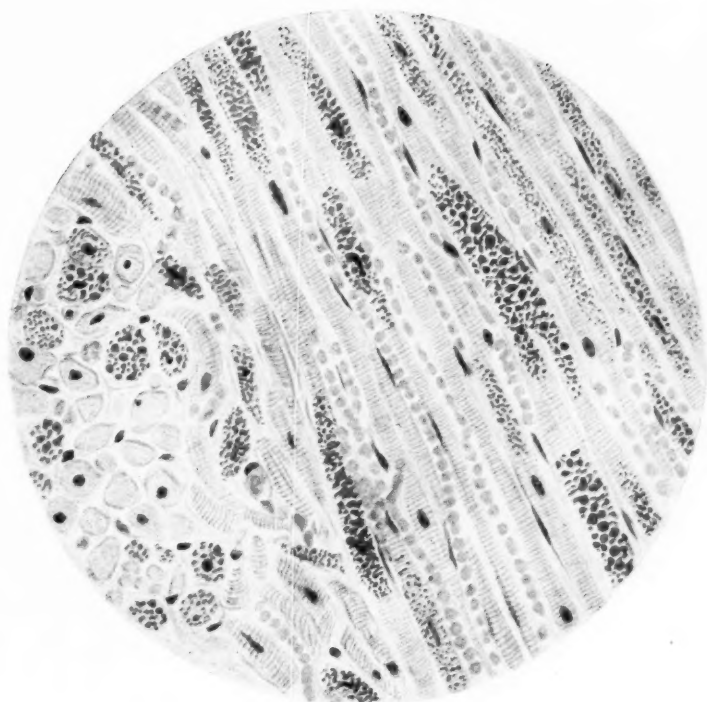
<i>Auricular Extra-systoles (5).</i>			
Case.	Group.	Onset.	Duration.
J. H.	I	9th day	4 days
F. L.	I	9th "	1 day
R. S.	II	18th "	2 days
C. M.	II	18th "	74 days
H. L.	III	20th "	6 "
<i>Ventricular Extra-systoles (11).</i>			
E. Y.	III	?	
G. C.	III	?	
H. L.	III	20th day	6 days
M. R.	III	9th and 24th days	2 "
N. C.	II	16th day	18 "
A. H.	II	24th day	36 "
R. S.	II	18th and 19th days	26 "
G. R.	II	27th day	short period
C. M.	II	18th day	1 day
M. T.	II	9th and 12th days	2 days
V. L.	II	?	short period
<i>Auricular Flutter (2).</i>			
E. P.	I	11th day	1 day
J. H.	I	12th "	1 "
<i>Paroxysmal Tachycardia (1).</i>			
A. S.	II	41st and 51st days	2 days
<i>Auricular Fibrillation (1).</i>			
E. J.	I	7th and 8th days	2 days
<i>Auricular Fibrillation and Heart-block (3).</i>			
V. T.	I	7th day	1 day
E. P.	I	8th and 10th days	2 days
J. M.	I	7th day	1 day
<i>Heart-block (1).</i>			
F. L.	I	12th day	1 day
<i>Nodal Extra-systoles (1).</i>			
A. H.	II	24th day	36 days
<i>Nodal Rhythm (3).</i>			
E. J.	I	6th day	1 day
J. M.	I	10th day	1 "
E. P.	I	8th and 10th days	2 days
<i>Reversal of Nodal Beats (1).</i>			
R. S.	II	18th day	1 day

DESCRIPTION OF PLATES.

PLATE 1. Ventricular muscle stained with Sudan III and haematoxylin. Accumulation of fat in muscle fibres seen in four cases of Group I.

PLATE 2, FIG. 1. Microphotograph of ventricular muscle stained with haematoxylin and Sudan III. The dark areas are muscle cells more or less completely filled with fat.

FIG. 2. Ventricular muscle showing a central patch of myocarditis.



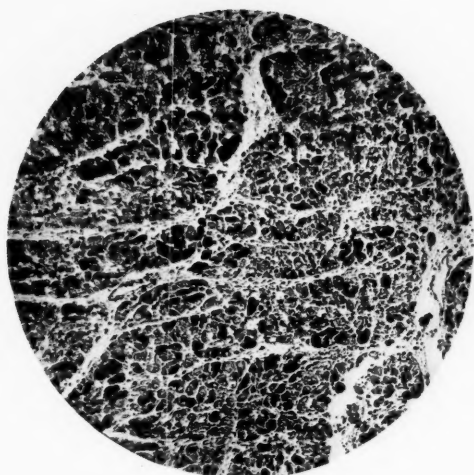


FIG. 1

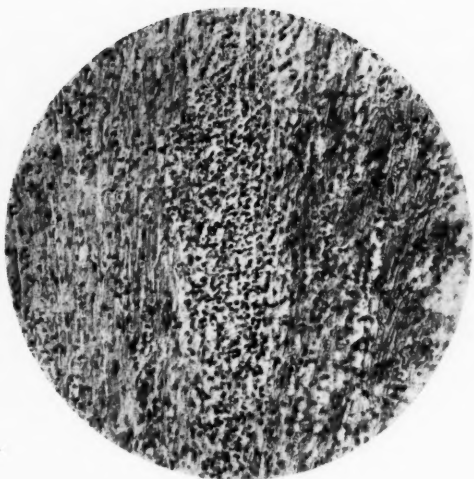


FIG. 2

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THE EFFECTS OF ANAEMIA UPON THE PATHOLOGICAL PROCESSES OCCURRING IN ACUTE ULCER OF THE STOMACH¹

By C. BOLTON

(From the Research Laboratories, University College Hospital Medical School)

With Plates 3 and 4

THIS paper deals with clinical observations upon, and an experimental investigation into, the supposed influence which anaemia exerts upon the formation and the fate of acute gastric ulcer.

For many years anaemia has been believed to be an important factor in the aetiology of ulcer of the stomach, and perhaps most present-day writers are still in agreement with this supposition. The hypothesis is based upon clinical and experimental evidence, and before detailing my own observations I shall give some account of this evidence.

The *clinical* evidence is unsatisfactory and appears to me to rest upon very uncertain grounds. The chief arguments in favour of this view are: (1) that chlorosis or anaemia is frequently associated with ulcer of the stomach; (2) that a history of anaemia may commonly be obtained in the subjects of gastric ulcer; and (3) that young females are particularly liable to be attacked by the last-named disease.

1. It is undoubtedly true that anaemia is very commonly present in the subjects of gastric ulcer, but this combination by no means proves that the anaemia is concerned in the production or propagation of the ulcer, because it is a fact that all ulcers during their formation or extension are constantly giving rise to haemorrhage; if not detectable by the naked eye, at any rate to be found in the stomach contents or faeces by chemical tests. A considerable degree of anaemia usually results from such a loss of blood. The association of chlorosis, which is a disease distinct from secondary anaemia, and gastric ulcer is less frequent, and as a fact very few of the cases of ulcer which I have seen have shown such a combination.

The chief errors which are responsible for the supposition that gastric ulcer commonly complicates chlorosis appear to be that the diagnosis of anaemia and chlorosis is sometimes made without any examination of the blood; that the

¹ The expenses of this research have been defrayed by a grant from the Graham Research Fund, University of London.

tendency is to diagnose chlorosis in most young women suffering from 'anaemia'; and that the clinical diagnosis of gastric ulcer is too frequently made in young females who are suffering from gastric pain, because it has been proved that the subjects of anaemia or chlorosis commonly suffer from pain and vomiting, which are indistinguishable from similar symptoms due to gastric ulcer. Such symptoms occurring in a young woman may merely indicate gastric irritability, or on the other hand a form of interstitial gastritis in which the mucous membrane of the stomach is swollen and easily bleeds, so that haematemesis is a superadded symptom, in which event it is impossible by a consideration of the clinical aspect of the case only to exclude the presence of an ulcer of the stomach (1).

2. The evidence based upon a previous history of chlorosis or anaemia is less reliable still, because, although the patient may undoubtedly have suffered from one of these diseases, there is no guarantee that the ulcer commenced at the time when the patient was so suffering, since the duration of the patient's gastric symptoms by no means indicates the duration of the ulcer. The evidence of the presence of chlorosis in Crisp's five cases of gastric perforation in females under 23 years is very slender. Crisp (2) in 1843 was the first observer to initiate the idea that chlorosis associated with menstrual irregularities is the chief predisposing cause of gastric ulcer. The evidence of chlorosis in four of his cases was based upon the statements of others as to the pale appearance of the patients and the fact that the menstruation was irregular in two of them. The case which he himself had previously seen was said to be 'delicate looking' and the menstruation was also irregular. He collected together the records of forty-six further cases of perforation, making fifty-one in all, and found that thirty-nine were females, of whom thirty-one were under 25 years of age, and twelve were males.

Later writers have published more accurate records in that anaemia was proved to exist by examinations of the blood, but they have failed for the above reasons to establish the point at issue. It does not come within the scope of this paper to give further details of these publications.

3. Finally, in speaking of the age and sex incidence of gastric ulcer the majority of writers merely state that the disease is most commonly found in young females between the ages of 20 and 30 years. This statement is not particular enough, when one is concerned with exact investigations into the aetiology of ulcer, because we know that there are several types of this disease. Aetiologically speaking, there are several forms of chronic ulcer, depending upon their different origins from distinct types of acute ulcer. The fact is that young females are particularly liable to a certain type of acute ulcer, which very commonly heals, or which may develop into chronic ulcer. The point at issue is whether or not anaemia or chlorosis is in any way connected with the origin or development of this type of acute ulcer. The onus of proving this rests with those who believe in such a connexion. My own observations upon acute ulcer verified at autopsy indicate that there is no such close connexion.

The *experimental* evidence, which is accepted as confirmatory of the hypothesis of this relationship of anaemia and gastric ulcer, is not very weighty. It is impossible to produce chlorosis in an animal, so that experiments can only deal with the effects of a secondary anaemia.

The earliest experiments are those of Quinke and Daettwyler (3). These observers performed two experiments upon dogs. A gastric fistula was made in the first case, and through this perchloride of iron was injected into the submucous tissue of the stomach in order to produce an ulcer. This ulcer healed in eighteen days. The dog was then repeatedly bled and thus rendered anaemic. A second ulcer was produced by the same means as before, and after thirty-one days was not yet healed. An ulcer was produced in the second case through a gastric fistula by touching the mucous membrane with a hot iron, and was found to heal in a 'few' days. When the animal was rendered anaemic and a second ulcer produced as before, it had not yet healed after twelve days. They concluded that ulcers were produced by slighter injuries of the mucous membrane and more easily in anaemic animals, and that such ulcers healed with greater difficulty than in normal animals.

Silbermann (4) experimented on three dogs. His ulcers were produced by the injection of a suspension of chromate of lead into a gastric artery, by tying small vessels of the stomach, or by injuring the gastric mucous membrane. The animals were rendered anaemic by injection of pyrogallie acid, which destroys the red corpuscles and produces haemoglobinaemia. In the first case the ulcer perforated after four weeks, and in the other two cases the ulcers were not yet healed after three and five weeks respectively. He states that the ulcers of the control animals *usually* healed in three weeks, so that there was evidently some variation in the time of healing in these animals. He concluded that the anaemic condition had given rise to progressive ulceration of the stomach.

Litthauer (5) experimented on eight dogs, of which one died the next day and in another no ulcer was produced, leaving six positive results. The ulcers were produced by excision of pieces of mucous membrane or by scalding with hot water. The animals were rendered anaemic by the injection of pyrocin in four and pyrogallie acid in two cases.

Only two of the cases are of interest in this connexion, because the other four were fed with either a 0.37 or a 0.5 per cent. hydrochloric acid solution in addition. Of the two former cases one presented a scar on the forty-second day and the other an open ulcer on the nineteenth day. Scars were found on the twelfth, forty-ninth, fifty-ninth, and sixty-third days respectively in the four latter cases. From the character of the scars Litthauer concluded that the ulcers had been deeper and remained unhealed for a longer time than usual. He, however, disagreed with Silbermann's opinion that anaemia gives rise to a progressive ulceration.

Finally, Suzuki (6) by the injection of silver nitrate solution into the wall of the stomach produced ulcers in eight dogs, anaemia being established by the subcutaneous injection of pyrocin before or after the formation of the ulcers.

The animals died or were killed at varying periods from two to eighty-four days. He also employed fourteen control experiments. He concluded that the influence of this anaemia in its ability to retard the healing of the ulcers was not proved.

The above short résumé of the experimental evidence shows that the utmost which can be claimed is that a delay, amounting to not more than a certain number of days, in the healing of an acute ulcer or of an injury of the stomach may result from anaemia produced by bleeding or the injection of poisons which destroy the blood. The method of the injection of poisons is open to the objections that no similar condition occurs in the human being, and that the results cannot be applied to human pathology, because one cannot say how much of the effect produced is due to the poison itself and how much to the anaemia, particularly as haemoglobinaemia is also present. The more an experiment approximates to the conditions of human disease the more valuable it is. As I have before remarked, it is impossible to produce chlorosis in an animal, but quite easy to bleed it, and anaemia due to loss of blood is a constant accompaniment of chronic ulcer and extremely common during the formation and extension of acute ulcer in the human being. Quinke's experiments were too few in number and his methods of producing ulcers, particularly through a gastric fistula, not of the best.

None of the observers have paid any attention to the diet of their experimental animals, which in my opinion is a point of importance, because I have shown that irregularities in healing take place when the animal is fed on a meat diet (7). The prolonged action of the gastric juice on such a diet is apt to cause necrosis of the granulation tissue of the base of the ulcer, so that its healing may be delayed. Of course one cannot expect all ulcers to heal in quite the same time, but I found that on a milk diet the healing of experimental gastric ulcers was more uniform, and that therefore the ulcers at their various stages were more comparable with each other.

Neither is it a safe practice, as was done in some of the above-mentioned cases, to judge of the previous condition of the ulcer and of its duration by the scar which it has left. The correct method is to compare the ulcers of anaemic animals with those of controls of precisely the same duration and at the various stages in their development and healing.

The problems which can be experimentally solved and directly applied to human pathology are: (1) Is the effect upon the gastric cells of anaemia, due to loss of blood, of such a nature that the production of an acute ulcer will be facilitated, and that such an ulcer will be more extensive than one produced similarly in a healthy animal? (2) Is the vitality of the gastric cells or of the connective-tissue base of the ulcer so affected by anaemia that the gastric juice will cause spreading laterally or in the depth of the ulcer? (3) Is the vitality of one or both of these two structures so affected that the healing of the ulcer is arrested or delayed?

Clinical Observations.

My attention was particularly directed to the effects of anaemia by the clinical observation, which I have already recorded, that when a patient suffering from acute gastric ulcer died of haemorrhage, the ulcer was in all cases in which the patient had survived for a certain length of time found to be healing at its edges, and that the extent of the healing varied with the length of life of the patient. In some cases the healing had advanced so far that the bleeding vessel appeared to open in the centre of a scar. Some of these cases have already been published (8), and I now give a complete list of the cases I have observed up to the present time.

Case I. Female, servant, aged 30 years. No previous gastric symptoms. Sudden onset of haematemesis. Died on the sixth day after the first bleeding. Recent acute ulcer of the size of a threepenny piece at the cardiac end of the stomach. Cardiac edge of ulcer cicatrizing. Open mouth of an artery in the base of the ulcer.

Case II. Female, aged 43 years. No previous gastric symptoms. Pain and vomiting for some days, followed by sudden haematemesis. Died on the twenty-first day after the first bleeding. Recent acute ulcer at the cardiac end of the stomach, advanced in healing at one side.

Case III. Female, aged 27 years. Two previous attacks of pain and haematemesis, seven and three years ago respectively. Pain for three days followed by haematemesis. Died on the eighteenth day after the first bleeding. Recent acute ulcer the size of a barley-corn about the centre of the stomach and near the small curvature on the posterior wall. Healed almost up to the open mouth of an artery. Three scars of acute ulcers also present (Fig. 1).

Case IV. Male, labourer, aged 49 years. An attack of pain and vomiting seven years previously; since this, constant indigestion. Onset with sudden haematemesis. Died on the eighteenth day after the first bleeding. Recent acute ulcer 5 mm. in diameter on the small curvature in the pyloric region. Rapidly healing, and an open vessel in the centre of the base. Near this ulcer was a scar of a former acute ulcer. Small acute duodenal ulcer also healing.

Case V. Female, nurse, aged 69 years. Previous attack five months ago. Sudden onset of haematemesis, following a 'bilious attack' with pain a fortnight before. Died on the eighteenth day after the bleeding commenced. Four cicatrized acute ulcers near the small curvature to the pyloric side of the centre of the stomach. A small hole in the centre of one scar opening into an artery.

Case VI. Male, moderate drinker, aged 68 years. 'Indigestion' and pain in the lower part of the chest for years, and one previous attack of bleeding nineteen years before. Death on the seventeenth day after the commencement of a second attack of haematemesis. Acute ulcer advanced in healing with a large open vessel in its base on the small curvature one inch from the cardiac orifice; also scars of five previous acute ulcers near this.

Case VII. Female, married, aged 44 years. Three previous attacks of 'indigestion', ten, five, and two years ago respectively. Sudden onset of haematemesis following pain of one day's duration. Death on the fifth day of the haemorrhage. Recent acute ulcer on the centre of the small curvature, healing.

Case VIII. Female, married, aged 35 years. Pain and flatulence for many years. Haematemesis six years previously. Death on the twenty-fourth

day of the haemorrhage. Two scars on the centre of the posterior wall of the stomach midway between the small and large curvatures. One completely healed and the other almost completely, the centre presenting an opening into a vessel. Their sizes were about $\frac{1}{2}$ by $\frac{1}{2}$ inch. A small scar on the small curvature on the pyloric side of the mid line.

Case IX. Male, oilman, aged 56 years. History of 'indigestion' and epigastric pain for three years. Death fifteen days after the bleeding commenced. Acute ulcer about $1\frac{1}{2}$ by $\frac{3}{4}$ inch in size on the small curvature $2\frac{1}{2}$ inches from the cardiac orifice, healing. One side showed a stellate scar. An open vessel near one edge.

Case X. Male, woodcutter, aged fifty-one years. Pain in the lower part of the abdomen for one month. Death on the sixteenth day of an attack of haematemesis. Acute ulcer, which had been extending, size $1\frac{3}{8}$ by $1\frac{1}{8}$ inches, about the centre of the small curvature. Healing all round. A bleeding vessel in the centre.

Case XI. Male, porter, aged 42 years. Indigestion for years. Severe pain and vomiting for one year. Died on the eighth day of the bleeding. Acute ulcer, which had been extending, on the small curvature $1\frac{1}{2}$ inches from the pylorus, size $\frac{1}{2}$ by $\frac{3}{4}$ inch. Advanced in healing all round. Surrounding mucous membrane puckered. An open vessel in the centre of the ulcer.

Case XII. Female, married, aged 45 years. Haematemesis seven months ago. Pain and vomiting commenced three weeks before the second haematemesis, and death occurred on the eighth day of the bleeding. Acute ulcer on the posterior wall near the centre of the small curvature. The edges were healing and the base, in which a bleeding vessel was situated, was filling up. Two small radiating scars were found on the small curvature.

These observations show that in spite of repeated haemorrhages, which are sufficiently profuse to bring about the death of the patient, acute ulcer of the stomach in the human being heals rapidly and in the normal manner when placed under suitable conditions. Such conditions are those which ensure rest for the stomach both in regard to the secretion of gastric juice and to the movements of the organ. Such patients are kept absolutely at rest and fed by the rectum till the bleeding has stopped, and then on small amounts of liquid food very gradually increased, so that the work done by the stomach is at a minimum in the first instance and increased gradually. There is no reason to doubt that, when the patient survives, healing similarly occurs in the vast majority of cases. Delay or arrest of the healing process rather occurs in those cases which do not bleed and are therefore not recognized, so that their disorders of gastric secretion and movements are not corrected by appropriate dieting and rest. It is to be noted that none of the above patients were suffering, or had suffered, from chlorosis.

The degree of anaemia present in cases of haemorrhage from acute ulcer naturally varies very considerably. The red corpuscles may not even be diminished to 3,000,000 per c.mm., but, on the other hand, counts of 1,000,000 or even less may be seen. In most cases of chronic ulcer the red corpuscles are not as a rule diminished below 4,000,000 per c.mm. except in the case of a recent severe haemorrhage, or if such is frequently repeated.

Experimental Investigation.

Experiments have been conducted with the view of ascertaining what influence, if any, anaemia due to loss of blood is able to exert upon the formation, the spread, and the healing of acute ulcer of the stomach.

Method. In all the experiments cats were used. The ulcers in the anaemic animals were compared at the different stages of their evolution and cicatrization with similar ulcers in control animals.

Acute ulcers were produced in the animals by the injection into the anterior gastric wall about its centre of an immune serum of the goat, the animals in all cases being under the influence of ether at the time of injection.

This gastrototoxic serum was formed by immunizing the goat with the gastric cells of the cat, and for the details of the method of production of the serum, of the injection into the cat, and of the formation of the ulcer the reader is referred to the *Proceedings of the Royal Society*, B, vol. 82, p. 233.

This method of producing an ulcer is more nearly comparable to the mode of formation of acute ulcer in the human being than is the method of injecting solutions of salts, which cause necrosis of whatever living tissues happen to be exposed to their action. As I demonstrated some years ago, the poison contained in gastrototoxic serum is to a great extent specific for the gastric mucous membrane, its action upon other living tissues being much more limited in degree. It is rapidly taken out of solution by the gastric cells, for which it has an especial affinity, saturation of the serum with gastric cells in the test-tube depriving it of its toxicity in half an hour or even less (9). Further, the gastric juice is a necessary co-operative factor in the formation of the ulcer, because if it be put out of action the poison, although fixed to the cell, is unable to cause its death (10). The normal blood serum of the goat is without action when similarly injected into the cat's stomach wall, so that in gastrototoxic serum one has a poison which is suspended in a neutral fluid closely approximating in composition to the body fluids of the animal injected. The poison is rapidly taken out of solution and fixed by the overlying mucous membrane and the tissues which the serum is infiltrating, and the neutral fluid is absorbed without producing any further harm on the surrounding tissues. There is, therefore, produced no widespread affection of the tissues which would impede their power of repair.

In all experiments of this kind it is of great importance to inject control animals with the same serum which is used to produce the ulcers in the experimental animals, because the extent and depth of the ulcers vary in proportion to the strength of the serum, which alters during the process of immunization.

In order to make the ulcers strictly comparable the diet of the animals was carefully attended to, because, as I have previously stated, when fed on a meat diet irregularities in the healing of the ulcers occur, whereas on a milk diet the

latter is rendered as uniform as it is possible to be made. When fed on a meat diet during the formation of the ulcers, the necrotic tissue is rapidly separated, whereas when milk forms the diet the ulcers take longer to form. This effect is entirely due to the more efficient and prolonged action of the gastric juice in meat-fed animals. In these experiments, therefore, the diet of the animals for the first four days has consisted of meat, so as to secure a rapidly formed ulcer, and after this period exclusively of milk, so as to ensure as great a uniformity as possible in the healing of the ulcers. On such a diet towards the end of the second week the base of the ulcer is covered by granulation tissue and the deeper layers, including the peritoneum, have become fibrous. On the sixth or seventh day the edges of the ulcer have become rounded and smooth, owing to a covering of a single layer of cells proliferated from the adjoining gland cells. On the tenth or eleventh day this surface layer has also extended a little way over the base of the ulcer and rudimentary glands have commenced to form from the surface epithelium and to burrow down into the cellular stroma. At the end of the third week the base is completely or almost completely covered with epithelium, and the granulation tissue has largely become fibrous (7).

The anaemia was induced by abstraction of blood from the femoral or carotid artery, the animal on each occasion being anaesthetized with ether. The number of red blood corpuscles in the normal cat varies from about 10,000,000 to 12,000,000 per c.mm., and the haemoglobin from 90 to 110 per cent. This variation, together with the differences in the weights of the animals, accounts to some extent for the different degrees of anaemia produced by the bleedings. The volume of the cat's blood varies according to the weight of the animal from 91.18 c.c. for a 2460 gm. cat to 140.22 c.c. for a 3520 gm. cat. In one case (Exp. 27) 227 c.c. of blood were removed from a 3459 gm. animal in twenty-four days. This represents an amount only about 40 c.c. less than twice the normal volume of the blood.

SERIES I.

Exp. 1. Wt. 2870 gm. Three bleedings at intervals of two days; 50 c.c., 34 c.c., and 27 c.c. being respectively abstracted on these occasions. On the seventh day the cat weighed 2410 gm.; 6 c.c. gastrototoxic serum injected. Died on the following day. An ulcer about half an inch in diameter was forming in the stomach.

Exp. 2. Wt. 2520 gm. Three bleedings at intervals of two days; 50 c.c., 40 c.c., and 35 c.c. being respectively abstracted on these occasions. On the seventh day the cat weighed 1850 gm.; 6 c.c. gastrototoxic serum injected. Killed six days later. A healing ulcer about $\frac{3}{4}$ inch by $\frac{1}{2}$ inch in size was present in the stomach (Fig. 2).

Microscopical examination. The edge of the ulcer was rounded and smooth from the growth of epithelium over it. The latter was growing round the incurved edge of the ulcer on the base, which was completely uncovered by epithelium. The ulcer extended more than half-way through the muscular coat of the stomach and its base was covered with a thick layer of necrotic tissue.

Controls.

Exp. 3. Wt. 3200 grm. Injected with 6 c.c. gastrototoxic serum, and killed after forty-eight hours. An ulcer very slightly larger than, but of the same appearance as, that of *Exp. 1* was forming in the stomach

Exp. 4. Wt. 3750 grm. Injected with 6 c.c. gastrototoxic serum. Killed six days later. A healing ulcer of the same size and appearance as that of *Exp. 2* was present in the stomach (Fig. 3).

Microscopical examination. The edge of the ulcer was rounded, smooth, slightly incurved, and covered with a single layer of epithelial cells, which were beginning to grow on to the base to exactly the same degree as in *Exp. 2*. The ulcer extended more than half-way through the muscular coat and its base was covered with a thick layer of necrotic tissue.

It is quite clear from these experiments that a previous and very considerable loss of blood does not affect the formation of an ulcer either in its superficial extent or depth; and that the regeneration of the epithelium on the sixth day will be found to have advanced to the same degree in the anaemic as in the normal animal.

SERIES II.

Exp. 5. Wt. 2420 grm. Injected with 10 c.c. gastrototoxic serum. Three days later 45 c.c. blood abstracted. Died two days later. An ulcer about 1 by $\frac{3}{4}$ inch in size forming in the stomach.

Exp. 6. Wt. 3120 grm. Injected with 10 c.c. gastrototoxic serum. Three days later 50 c.c. blood abstracted. Died two days later. An ulcer with a perforation in the base about $\frac{3}{4}$ inch across was present in the stomach.

Exp. 7. Wt. 2420 grm. Injected with 10 c.c. gastrototoxic serum. Seven days later 40 c.c., and three days later 30 c.c., blood abstracted. Killed on the thirteenth day after the injection. A healing ulcer of the size of $\frac{1}{2}$ by $\frac{1}{4}$ inch was present in the stomach. The edges were smooth, rounded, and slightly incurved.

Microscopical examination. The edges were covered with a single layer of epithelial cells which in places had commenced to form small glands. The layer of cells had grown round the incurved edge of the ulcer and on to the base for a certain distance. The base was formed of granulation tissue covered with a thin necrotic layer (Fig. 4).

Controls.

Exp. 8. Wt. 3170 grm. Injected with 10 c.c. gastrototoxic serum. Died four days later. An ulcer about $\frac{3}{4}$ by $\frac{3}{4}$ inch in size was found in the stomach, similar in all respects to the ulcer of *Exp. 5*.

Exp. 9. Wt. 2760 grm. Injected with 10 c.c. gastrototoxic serum. Killed three days later. An ulcer about 1 by $\frac{3}{4}$ inch in size and quite similar to that of *Exp. 8* was present in the stomach.

Exp. 10. Wt. 2620 grm. Injected with 10 c.c. gastrototoxic serum. Killed on the thirteenth day after injection. A healing ulcer about $\frac{3}{4}$ inch in diameter with smooth rounded edges was found in the stomach.

Microscopical examination. The edges were covered with epithelium, which was commencing to form glands and which had grown round the incurved edge of the ulcer, but not quite so far on to the base as in Exp. 7. The edge was more overhanging than in that experiment. The base was formed of granulation tissue covered with a thin necrotic layer (Fig. 5).

The early ulcers in the anaemic and the normal animals were in the same condition. The fact that one of the ulcers in the former animals perforated goes for nothing, because when one injects such a large volume of serum and the ulcers extend deeply it is largely a question of chance whether the base happens to rupture, and such a rupture does not indicate a progressive ulceration. The ulcers in the two animals which were killed on the thirteenth day were in precisely the same stage of healing both with regard to the regeneration of the epithelium and the growth of the granulation tissue of the base.

SERIES III.

Exp. 11. Wt. 2600 grm. Injection of 11 c.c. gastrototoxic serum and at the same time 30 c.c. blood abstracted. Died in two days. A large ulcer forming in the stomach.

Exp. 12. Wt. 2650 grm. Injection of 11 c.c. gastrototoxic serum and at the same time 30 c.c. blood abstracted. Died in three days. A large perforated ulcer found in the stomach.

Exp. 13. Wt. 3170 grm. Injection of 11 c.c. gastrototoxic serum and at the same time 50 c.c. blood extracted. Bled on the sixth and thirteenth days, 30 c.c. being removed on the former and 20 c.c. on the latter occasion. Died on the seventeenth day. A healing ulcer was present in the stomach.

Microscopical examination showed that the edges and a broad ring round the periphery of the base were covered with a layer of epithelial cells, leaving an uncovered area of healthy granulation tissue in the centre.

Controls.

Exp. 14. Wt. 2820 grm. Injection of 11 c.c. gastrototoxic serum. Died five days later. A large perforated ulcer similar to that in Exp. 12 was present in the stomach.

Exp. 15. Wt. 2830 grm. Injection of 11 c.c. gastrototoxic serum. Killed on the twenty-first day. A healed ulcer was found in the stomach, the base of which on microscopical examination was found to be completely covered by a single layer of epithelial cells.

This series of experiments shows that an ulcer in an anaemic animal on the seventeenth day is in the same advanced condition of healing as would be found in a normal animal, only the central area of the base being uncovered by epithelium. This uncovered area is composed of healthy granulation tissue.

SERIES IV.

Exp. 16. Wt. 2950 grm. Injection of 9 c.c. gastrototoxic serum and at the same time 30 c.c. blood abstracted. The animal was bled subsequently at intervals of six, five, and seven days; on the three occasions 30 c.c., 15 c.c., and

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25 c.c. blood were removed. Killed on the twenty-second day after injection. On this day the red blood corpuscles numbered 7,600,000 per c.mm. and the haemoglobin was 60 per cent. A healed ulcer was present in the stomach, the base of which was completely covered by a single layer of cells (Fig. 6).

Exp. 17. Wt. 3020 grm. Injection of 9 c.c. gastrototoxic serum and at the same time 30 c.c. blood abstracted. Six days later 10 c.c. blood were removed and the animal died on the following day. A perforated ulcer was found in the stomach.

Exp. 18. Wt. 3230 grm. Injection of 9 c.c. gastrototoxic serum and at the same time 35 c.c. blood abstracted. The animal was bled six and again nine days later, 35 c.c. on the former and 30 c.c. blood on the latter occasion being removed. It was killed on the twenty-second day. On the day of death the red blood corpuscles numbered 7,760,000 per c.mm. and the haemoglobin was 70 per cent. A healed ulcer was present, the base of which was completely covered by a single layer of cells (Fig. 7).

Exp. 19. Wt. 3000 grm. Injection of 9 c.c. gastrototoxic serum and at the same time 35 c.c. blood abstracted. The animal was bled twice as in Exp. 18, the same amounts of blood being removed. It was killed on the twenty-second day, the red blood corpuscles numbering 3,760,000 per c.mm. and the haemoglobin being 40 per cent. An ulcer was present in the stomach. The base was covered by a single layer of cells except a very small area in the centre.

Controls.

Exp. 20. Wt. 2470 grm. Injection of 9 c.c. gastrototoxic serum. The animal was killed on the twenty-second day. An ulcer was present of exactly the same size as in Exp. 19. The base was covered by a single layer of cells except a very small area in the centre of the same size as that in Exp. 19 (Fig. 8).

Exp. 21. Wt. 3150 grm. Injection of 9 c.c. gastrototoxic serum. The animal was killed on the twenty-second day. A healed ulcer was present in the stomach, its base being completely covered by a single layer of epithelial cells.

It is quite obvious from these experiments that anaemia has no effect whatever in retarding the healing of an acute gastric ulcer. A further series of experiments was conducted in which a smaller dose of serum was injected, and the animals were bled to a greater extent and allowed to eat meat during the healing stage, the effect of which, as I previously showed, is that in about three out of five cases a thick layer of necrotic tissue is found in the centre of the base of the ulcer on the twenty-first day.

SERIES V.

Exp. 22. Wt. 3200 grm. Bled to the extent of 30 c.c. Two days later 6 c.c. gastrototoxic serum injected and at the same time 30 c.c. blood removed. The animal was bled on five subsequent occasions at intervals of five, four, six, three, and four days, the amounts abstracted being 30 c.c., 30 c.c., 35 c.c., 30 c.c., and 30 c.c. On the twenty-first day after injection it weighed 2825 grm., and its red blood corpuscles numbered 6,160,000 per c.mm., the haemoglobin being 48 per cent. The animal was killed on this day and a healing ulcer found in the stomach.

Microscopical examination showed that the epithelium had grown well on to the base of the ulcer, but there was a patch in the centre yet uncovered, the

epithelium having been prevented from further growth by necrosis of the granulation tissue of the base.

Exp. 23. Wt. 2400 gm. Bled to the extent of 30 c.c. Three days later 6 c.c. gastrototoxic serum injected and 20 c.c. blood removed. The animal was bled on five subsequent occasions at intervals of four, three, four, three, and seven days, the amounts abstracted being 20 c.c. on each occasion. On the twenty-eighth day after injection the animal weighed 2200 gm., and its red blood corpuscles numbered 3,280,000 per c.mm., the haemoglobin being 48 per cent. The animal was killed on this day and a completely healed ulcer found in the stomach.

Exp. 24. Wt. 2700 gm. Bled to the extent of 40 c.c. Three days later an injection of 6 c.c. gastrototoxin serum was given. The animal was bled on four subsequent occasions at intervals of four, four, five, and five days, the amounts removed being 30 c.c., 22 c.c., 30 c.c., and 33 c.c. On the twenty-third day the animal weighed 2515 gm., and its red blood corpuscles numbered 5,440,000 per c.mm., the haemoglobin being 40 per cent. It was killed on this day and a healing ulcer found in the stomach.

Microscopical examination showed that the healing had advanced as in Exp. 22, but was delayed by a patch of necrotic granulation tissue in the centre.

Exp. 25. Wt. 2515 gm. 30 c.c. blood was abstracted and three days later 6 c.c. gastrototoxic serum were injected. The animal was bled four days later to the extent of 30 c.c., and died on the ninth day following injection. An ulcer was present in the stomach; its base was adherent to the diaphragm except at one spot towards the edge where a perforation was situated. This experiment was of use in indicating the original size of an ulcer formed by injection of 6 c.c. serum of this particular strength.

Exp. 26. Wt. 3500 gm. Bled to the extent of 45 c.c. and at the same time 6 c.c. gastrototoxic serum injected. The animal was bled on three subsequent occasions at intervals of five, four, and six days, the amounts removed being 45 c.c., 50 c.c., and 40 c.c. On the twenty-first day the red blood corpuscles numbered 5,840,000 per c.mm., the haemoglobin being 50 per cent. The animal was killed on this day and a completely healed ulcer found in the stomach.

Exp. 27. Wt. 3450 gm. 40 c.c. blood removed and at the same time 6 c.c. gastrototoxic serum injected. The animal was bled on four subsequent occasions at intervals of four, four, six, and five days, the amounts removed being 50 c.c., 45 c.c., 45 c.c., and 50 c.c. On the twenty-fourth day the red blood corpuscles numbered 7,120,000 per c.mm., the haemoglobin being 42 per cent. The animal was killed on that day and a completely healed ulcer found in the stomach.

Controls.

Exp. 28. Wt. 3040 gm. An injection of 6 c.c. gastrototoxic serum was given and the animal was killed on the twenty-first day following. A completely healed ulcer was present in the stomach. The red blood corpuscles numbered 10,358,000 per c.mm., the haemoglobin being 80 per cent.

Exp. 29. Wt. 2045 gm. An injection of 6 c.c. gastrototoxic serum was given and the animal was killed on the twenty-fourth day following. A completely healed ulcer was present in the stomach. The red blood corpuscles numbered 10,040,000 per c.mm., the haemoglobin being 60 per cent.

The two anaemic animals in which the ulcers were not quite healed, owing to the granulation tissue in the centre of the base being necrotic on the surface, appear at first sight to show that the anaemia may have rendered the granulation tissue of the base less able to withstand the action of the gastric juice, because the fault was not in the epithelium. The irregularity in healing was, however, due to the diet, for these animals were purposely allowed meat to eat during the healing process.

Conclusions.

The whole series of experiments shows that when an animal, the subject of an acute gastric ulcer, is placed on a milk diet, so that its stomach empties rapidly, the growth of the epithelium over the base of the ulcer and the filling up of the latter with granulation tissue occurs with precisely the same regularity and at the same rate at all stages in the healing process whether the animal is anaemic or normal. When once the slough has separated from the base of the ulcer and healthy granulation tissue commenced to grow, the latter is no more vulnerable to the action of the gastric juice in the anaemic than in the normal animal. The same remarks apply to the regenerating epithelium, and, in addition, its activity of growth and power of forming new glands are not in the least interfered with by the anaemia.

Anaemia, therefore, produced by direct loss of blood, has no influence as an isolated factor in facilitating the production of an acute ulcer; nor in causing such an ulcer to extend laterally or in its depth by increasing the vulnerability of the tissues concerned; nor in preventing its healing either by interfering with the regenerative power of the surface epithelium or of that of the granulation tissue of the base of the ulcer. When the anaemic animal is allowed meat to eat, any delay in the healing is due to the diet of the animal and not to the anaemia.

These experimental facts agree with the clinical observations recorded above.

REFERENCES.

1. Bolton, 'Ulcer of the Stomach,' Lond., 1913, 243.
2. Crisp, *Lancet*, Lond., 1842-43, ii. 639.
3. Quincke and Daettwyler, *Correspondenzbl. f. Schweizer Aerzte*, 1875, iv. 101; and *Deutsch. med. Woch.*, 1882, xxv. 79.
4. Silbermann, *Deutsch. med. Woch.*, 1886, xxix. 497.
5. Litthauer, *Virch. Archiv f. Path. Anat. u. Physiol.*, Berlin, 1909, cxcv. 317.
6. Suzuki, *Archiv f. Klin. Chir.*, Berlin, 1912, xcvi. 632.
7. Bolton, *Proc. Roy. Soc. Med.*, Lond., 1910-11, iv. Path. Sect., 53.
8. Bolton, 'Ulcer of the Stomach,' Lond., 1913, Part iv, chap. i; and *Brit. Med. Journ.*, 1910, i. 1221.
9. Bolton, *Proc. Roy. Soc.*, Lond., 1905-6, B, lxxvii. 426.
10. Bolton, *Ibid.*, Lond., 1907, B, lxxix. 533.

DESCRIPTION OF FIGURES.

PLATE 3, FIG. 1. Micro-photograph of a section of the acute ulcer from Case III. On the extreme right is the artery in the centre of the base of the ulcer, and growing towards it is the newly formed mucous membrane. This consists of a very fine cellular stroma covered with a single layer of cubical cells, which are growing down in the form of tubular glands into the underlying tissue. As the mucous membrane approaches the artery it thins off into a single layer of flattened cells.

FIG. 2. Photograph of the ulcer from Exp. 2. This ulcer of an anaemic animal is of precisely the same size and in the same condition as that of the control animal shown in Fig. 3. It is six days old. The edge is rounded and incurved, and the base covered with necrotic tissue.

FIG. 3. Photograph of the ulcer from Exp. 4. It is six days old and from an otherwise normal animal. Its condition is the same as that of the ulcer shown in Fig. 2.

FIG. 4. Micro-photograph of a section of the edge of the ulcer from Exp. 7. The ulcer is thirteen days old and from an anaemic animal. The edge of the ulcer is incurved and covered with a single layer of cubical cells, which are growing down into the underlying cellular stroma in the form of tubular glands. The covering epithelium has grown round the incurved edge and for a short distance on to the base of the ulcer.

PLATE 4, FIG. 5. Micro-photograph of a section of the edge of the ulcer from Exp. 10. The ulcer is thirteen days old, from an animal otherwise normal, and is the control of the ulcer shown in Fig. 4. It is in exactly the same condition as the latter ulcer, except that the covering epithelium has not grown so far on to the base of the ulcer.

FIG. 6. Photograph of the healed ulcer from Exp. 16. It is twenty-two days old and from an anaemic animal. There is some puckering of the mucous membrane and in the centre of the scar is a small depressed area completely covered with epithelium.

FIG. 7. Micro-photograph of a section of the healed ulcer from Exp. 18. It is twenty-two days old and from an anaemic animal. The whole base is completely covered with epithelium, which on the left is forming new glands.

FIG. 8. Photograph of the almost healed ulcer from Exp. 20. It is twenty-two days old, from an animal otherwise normal, and is one of the controls of the ulcers shown in Figs. 6 and 7. There is some puckering of the mucous membrane, and in the centre of the scar a small area uncovered by epithelium, which shows black in the figure.



FIG. 1

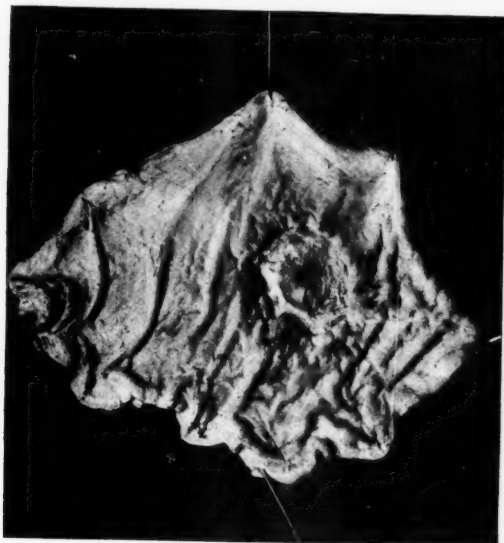


FIG. 2

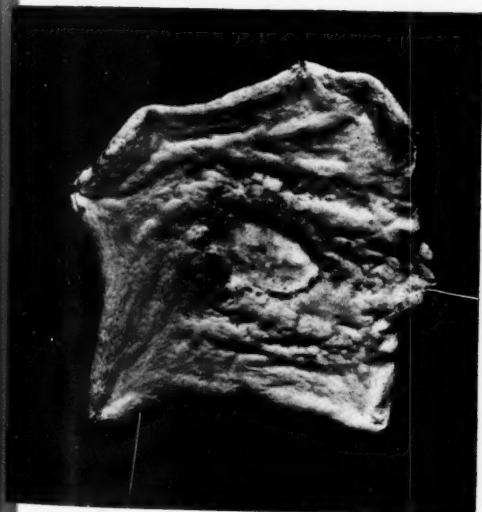


FIG. 3



FIG. 4

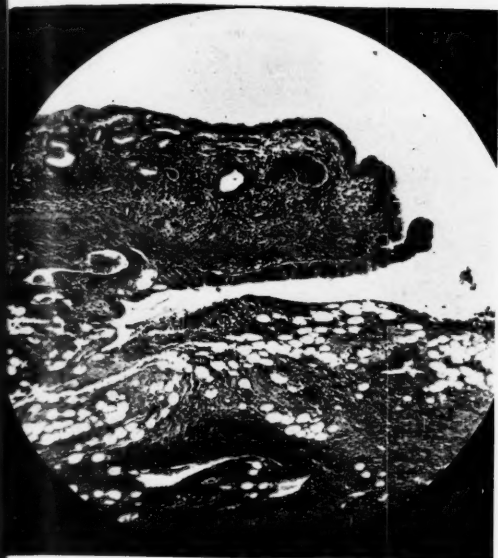


FIG. 5



FIG. 6



FIG. 7

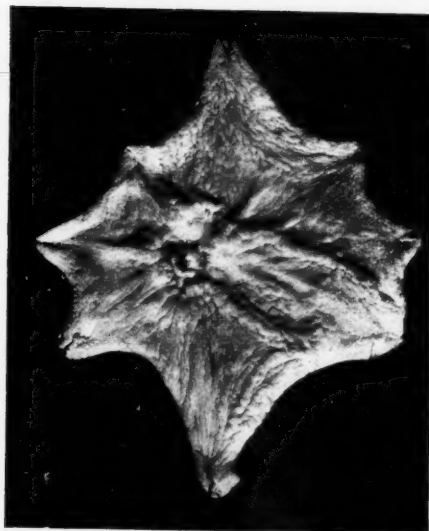


FIG. 8

CONDUCTION IN THE AURICLES

By A. E. NAISH

THE idea of a central conducting system of specialized neuro-muscular tissue leading right through from the sinus node to the termination of the Purkinje fibres in the ventricle would on *a priori* grounds seem probable, for in the early embryonic heart the auricular canal leads straight from the sinus to the ventricle, and the auricle is an outgrowth from this. So far histological evidence in favour of a specialized strand or strands of tissue connecting the sinus and Tawara nodes is unconvincing. Curran (2) and Thörel (6) have thought that they have found such connexions, but Aschoff (1), Mönckeberg (5), and Koch (4) have denied their existence. By means of their recent experimental investigations Eyster and Meek (3) have however obtained evidence in favour of the conduction of impulses between the two nodes taking place independently of the main body of the contracting auricular muscle. Testing dogs' hearts by the method of spread of electrical negativity, they have found that the excitation starts in the upper part of the sinus node, spreads rapidly throughout the node and to the neighbouring venous regions, but encounters resistance in its passage to the auricle across the sino-auricular junction, and in the great majority of cases reaches the Tawara node before it has spread to the body of the right auricle. In fourteen experiments the time taken in passing from the sinus node to the middle of the right auricle varied from 0.025 to 0.04 secs. Thus there is a definite *S-As* interval, occupying about quarter of the time of the *As-Vs* interval.

Clinical evidence in favour of or against a special path for conduction through the auricle is of necessity difficult to obtain, for there is no means of detecting the time of sinus excitation. Occasionally, however, tracings are difficult to explain on the supposition that conduction from the sinus to the ventricle takes place via the contracting auricular muscle, but become more intelligible if we suppose that the auricle is connected, so to speak, by a side chain to the conducting system, and that there is a definite *S-As* interval. That such an interval may be prolonged under pathological conditions seems very probable when we consider that dropped beats from sino-auricular block are a well-attested phenomenon.

The following case of acute heart-block accompanying typhoid fever and nephritis is brought forward as an example of the difficulty of explaining wholly

the tracings on the hitherto accepted theory of conduction. A brief general account of the case is first given, and then the tracings are examined without regard to chronological order.

Clinical Notes.

George M., aged 18, admitted to the Sheffield Royal Hospital on March 13, 1913.

Owing to the fact that his mother was also suffering from typhoid at the same time, and that the patient himself was too ill to answer questions, no full history of his illness was obtained; but it was ascertained that he had been in bed at home for eight weeks.

He appeared very ill on admission, face pallid, lips cyanosed, temperature 103°F ., respirations 32 per minute, pulse 120.

There was low delirium from time to time, but for the most part he lay quietly in bed without taking any notice of his surroundings. His bowels were constipated. The urine contained a large quantity of albumin and a little blood; the specific gravity was 1.012, and the quantity averaged over 1000 c.cm. per diem.

The blood gave a positive Widal reaction.

The heart showed some diffuse pulsation over the fourth and fifth left interspaces, but the apex beat was very indistinctly felt. The cardiac dullness extended from $1\frac{1}{2}$ inches to the right to $4\frac{3}{4}$ inches to the left of the mid-sternal line. The heart-sounds were very faintly heard, and unaccompanied by any murmurs.

There were dullness and crepitations at the bases of both lungs.

He remained in much the same condition for the next four days, the temperature varying between 100° and 103°F ., and the pulse between 120 and 140.

On March 17 the pulse fell to about 80 and became rather irregular, and at the same time the patient vomited, became very drowsy, and appeared almost moribund for a few hours.

During the next few days, though he vomited once or twice, his condition gradually improved; the urine contained decreasing quantities of albumin; the temperature came down slowly, after the 27th being seldom above normal; and the drowsiness diminished.

Between March 21 and April 1 the heart was nearly regular at the rate of about 50 per minute, and tracings showed that partial heart-block was present, the prevailing rhythm being 2:1. From April 1 onwards the normal 1:1 sequence became gradually more frequent and prolonged, though there were occasional relapses into 2:1 up to two weeks later.

Improvement continued, the albuminuria disappeared, and he was sent to a convalescent home on May 2.

Polygraph Tracings.

Fig. 1 is from a tracing taken on April 1, and is typical of what is seen over a considerable length of tracing taken on that day. It will be seen that sometimes the ventricular beats follow successive auricular beats, and that at other times the ventricle beats only once to every two auricular beats. Contrary to what one would expect, the $\Delta s-Vs$ intervals are not prolonged beyond the normal limit even in the beats immediately preceding the ventricular silences. This is quite exceptional; usually the interval is increased for a considerable time before

the occurrence of dropped beats, though in some cases recorded the increase does not occur until the last few beats before the silence.

Further, it will be seen that the *As-Vs* intervals of the beats following the ventricular silences are very short, certainly not exceeding 0.08 of a second, and sometimes much less. It is hardly credible that the impulse has passed from auricle to ventricle in so short a time. These ventricular beats may of course be escapes, but considerably longer pauses between the first few idio-ventricular beats would be expected, especially after so fast a ventricular rate immediately preceding, for it is when suddenly deprived of rapid auricular impulses that the

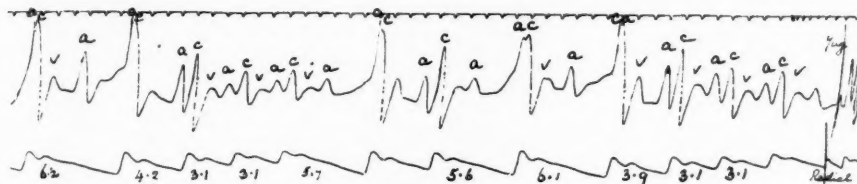


FIG. 1.

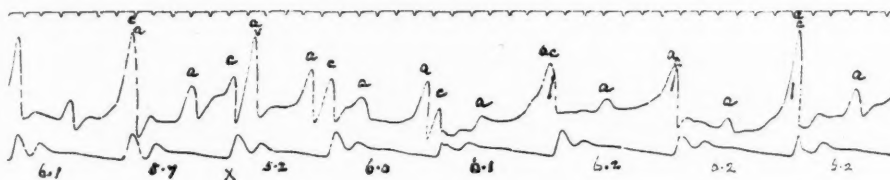


FIG. 2.

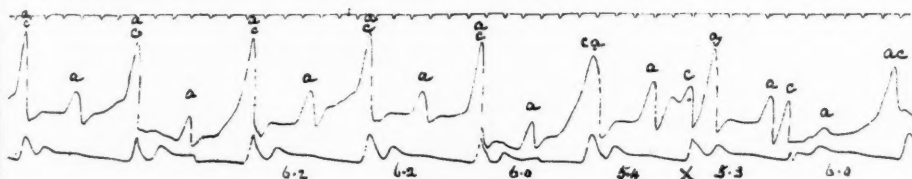


FIG. 3.

automatic action of the ventricle takes longest to develop. Further, this synchronism of *A* and *V* beats was a marked feature in tracings taken on every occasion on which any dissociation was present, although the auricular rate was by no means constant (see Fig. 3) and the repeated coincidence of the ventricular rate with a variable auricular rate would be very unlikely.

If on the other hand we consider that the sinus excitation passes by separate paths to the auricle and ventricle, and that in this case the *S-As* interval is pathologically prolonged, the explanation of the tracing becomes quite simple. For instance, if the *S-As* intervals were 1 sec., the *S-Vs* intervals before the dropped beats would be 0.3 sec., and those next after the dropped beats would be approximately 0.16 sec.

Figs. 2 and 3 are the halves of a continuous piece of tracing. Many yards of tracing taken on March 29 and 30 were almost exactly of this type. Throughout these lengths of tracing, for a number of cycles varying from six to twenty-eight, the ventricular beat is almost precisely synchronous with every second auricular beat; then follow two shorter cycles in which the *c* wave of the jugular pulse falls rapidly back nearer to the preceding *a* wave, and following this for the next three or four cycles the *As-Vs* intervals gradually diminish till they are finally lost again.

How are we to explain this tracing? If we suppose that the ventricular beats following the shorter pauses are responses to the auricular impulses immediately preceding them, then in the succeeding cycles there is an extinction of the *As-Vs* interval.

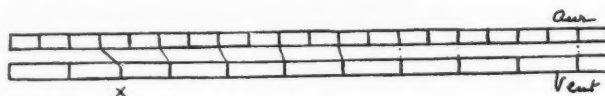


FIG. 4.

We may suppose that the ventricle begins to escape four or five cycles after the mark *x*, but against this explanation are some of the facts mentioned above in commenting on Fig. 1. Further, during the five cycles in which the *a* and *c* waves do not fall together the *As-Vs* interval is getting progressively shorter, for which there seems to be no explanation.

Another possible explanation is that the synchronous ventricular beats are responses to the preceding auricular impulses.

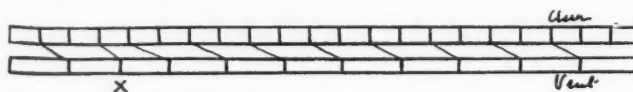


FIG. 5.

This would mean that the cycle immediately following the mark *x* was a cycle of 1:1 rhythm, and that the ventricular beat at the end of this cycle was derived from an auricular impulse that had taken 4.2-fifths, or nearly half a second, to reach the ventricle, another auricular beat having actually been completed before the previous one had excited the ventricle. Such a sequence can hardly be considered likely, especially if this tracing be compared with that shown in Fig. 1, where a similar explanation would border on the absurd. (It must be remembered that other tracings show almost every gradation between the condition shown in Figs. 2 and 3 and that shown in Fig. 1, so that the same explanation must probably apply to both.)

Adopting the supposition of a prolonged *S-As* interval and direct *S-V* conduction, the synchronous contraction of auricle and ventricle seen in Figs. 2 and 3 presents no difficulty, for the *S-V* conducting path has had twice as long to rest as the *S-A* path. On this supposition the cycle immediately preceding

the mark \times is a 1:1 cycle, the S - V interval lengthening out because of the short preceding pause.

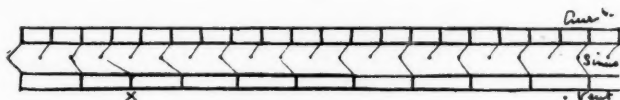


FIG. 6.

After this the $As-Vs$ intervals progressively diminish, since the conduction path to the ventricle is gradually recovering from the exhaustion of having responded to two successive sinus excitations.

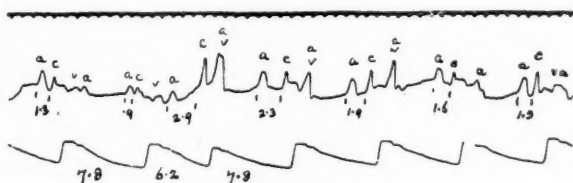


FIG. 7.

A similar progressive diminution of the *As-Vs* intervals after a single cycle of 1:1 rhythm is seen in Fig. 7, taken from another patient, in whom it was a frequently recurring phenomenon.

Summary.

Tracings are published from a case of acute heart-block, which receive a ready explanation only upon the supposition that the cardiac impulse spreads to the ventricle and to the auricle by different paths, and does not pass to the ventricle through the auricle, as hitherto supposed.

In conclusion, my best thanks are due to my colleague Dr. Arthur J. Hall for his kind permission to examine and report on this case.

BIBLIOGRAPHY.

1. Aschoff, *Centralbl. f. allg. Path. u. path. Anat.*, Jena, 1910, xxi. 433.
2. Curran, *Anat. Anzeiger*, Jena, 1909-10, xxxv. 89.
3. Eyster and Meek, *Heart*, Lond., 1914, v. 119.
4. Koch, *Archiv f. d. ges. Physiol.*, Bonn, 1913, cli. 279.
5. Mönckeburg, *Centralbl. f. allg. Path. u. path. Anat.*, Jena, 1910, xxi. 437.
6. Thorel, *Münch. med. Wochenschr.*, 1909, liv. 2. 2159.

OBSERVATIONS ON INSPIRATORY DIMINUTION OF THE PULSE (PULSUS PARADOXUS)

BY A. W. FALCONER AND JAMES M. McQUEEN

THE reduction in the volume of, or the complete disappearance of, the radial pulse on inspiration was first noted in 1850 by Williams. In 1854 Hoppe again drew attention to the phenomenon, and in 1859 Gerhardt described it as a sign of the onset of the asphyxial stage of croup.

It was not however until 1873, when Kussmaul described it as a valuable diagnostic sign in chronic adhesive mediastino-pericarditis and introduced the term 'pulsus paradoxus', that the subject gained general recognition. Since then a very considerable literature has grown round it and numerous explanations have been offered as to the mechanism of its production. As early as 1877 Sommerbrodt stated, without giving any explanation of the mechanism, that the pulsus paradoxus was a normal phenomenon and could be demonstrated in the great majority of individuals, more especially in individuals with powerful respiratory muscles, and least easily in those in whom the inspiratory muscles were weak and the expansion of the thorax limited. His statements at the time were not generally confirmed.

In the course of time, however, it was recognized that an inspiratory diminution of the pulse occurred in numerous conditions in addition to mediastino-pericarditis, more especially in conditions associated with laryngeal obstruction, with large pleuritic or pericardial exudates, with intrathoracic growths, following large haemorrhages and not infrequently in a marked form, in apparently perfectly normal individuals. In a small proportion of the cases the phenomenon has been limited to one side.

At the present time, although no satisfactory explanation of the phenomenon has been given in the pronounced cases occurring in normal individuals, the general consensus of opinion appears to be that the pulsus paradoxus has little, if any, diagnostic significance.

Brief reference may now be made to some of the many explanations which have been offered of the mechanism of the condition.

Kussmaul and many others considered the pulsus paradoxus a diagnostic sign of mediastino-pericarditis and due to a strangling of the big vessels at the base of the heart by adhesions rendered taut by inspiration.

Bäumler divided the cases of pulsus paradoxus into two groups: (1) those associated with a hindrance to the free air entry into the lungs producing

an increased negative pressure in the thorax, and (2) cases associated with mechanical hindrances brought into play or increased by inspiration. Both groups, he considered, might be accentuated by a weakened action of the heart.

With regard to class (1) he held that the increased negative intrathoracic pressure acting most strongly on the veins, pulmonary artery, auricles, and right ventricle produced in them and in the lung a blood-stasis which resulted in a diminution in the blood supply to the left ventricle, with a consequent weakening in the radial pulse.

Riegel demonstrated the occurrence of the *pulsus paradoxus* in many patients in whom there was no evidence of cardiac disease. It occurred chiefly in young convalescents and also in apparently sound if somewhat weak individuals. In these cases he observed on deep inspiration a definite diminution in the size of the pulse. In quiet breathing the phenomenon was little if at all present. Riegel considered the inspiratory diminution of the pulse depended upon an incomplete filling of the aortic system resulting from an increased negative intrathoracic pressure associated with the deeper inspiration.

He also considered that a degeneration of the cardiac muscle might act as a contributory cause. In a further paper he described the temporary appearance of a *pulsus paradoxus* following an intestinal haemorrhage in a typhoid patient.

In a still later paper Riegel recognized three classes of *pulsus paradoxus*: (1) cases associated with mediastino-pericarditis, in which he accepted Kussmaul's explanation; (2) cases associated with defective air entry giving rise to an increased negative intrathoracic pressure; (3) cases associated with cardiac weakness in which the normal inspiratory negative intrathoracic pressure was sufficient to cause the phenomenon.

Schreiber considered that the *pulsus paradoxus* met with in mediastinitis differed from the inspiratory diminution of the pulse seen in other conditions in the following points: (1) that there is a marked diminution in the volume or complete disappearance of the pulse of all arteries, and not only of the radial arteries, during inspiration, and more especially in the second half of inspiration; (2) that the true *pulsus paradoxus* does not require for its development the inspiration to be a deep one; (3) that the peculiar pulse intermission is accompanied by a regular action of the heart; (4) that the heart shows no weakening of its action during inspiration.

Rosenbach injected oil and air into the pleural cavity, and showed by massive injection so great a displacement of the heart and blood-vessels could be produced that the inspiratory descent of the diaphragm on one side, the other being thrown out of action by the fluid or air in the pleural space, produced an inspiratory kinking of the inferior vena cava. He attributed, therefore, the *pulsus paradoxus* in cases of massive exudates within the chest to insufficient filling of the heart resulting from intermittent obstruction of the inferior vena cava.

Franck and others have described the occurrence of *pulsus paradoxus* in persistent ductus arteriosus. They explain the inspiratory diminution of the pulse in these cases as a result of an inspiratory diminution of the pressure in the pulmonary artery permitting a freer flow from the aorta to the pulmonary artery during inspiration.

Reichmann, in 1904, summarized the literature and came to the conclusion that in all cases, the essential cause was a disturbance of the normal relationship between the arterial blood pressure and the respiratory variation in intrathoracic pressure leading to an actual or relative increase of inspiratory negative intrathoracic pressure.

Wenckebach attributes *pulsus paradoxus* in adherent pericardium to inspiratory traction on the heart embarrassing its action. He leaves the question open as to whether there is a direct traction on the aorta or the large veins.

Barr states that 'in cases of the *pulsus paradoxus* the systole of the left ventricle may be delayed or abolished for one or more beats owing to defect in the diastolic tension in the left ventricle, and the aspirating effect of the thorax causes a sudden emptying of the veins to fill the vacuum in the chest, and with the removal of the obstruction to the capillary flow there is a simultaneous depletion of the arteries. In the former case a weak right heart and a large lung reservoir are important factors, and in the latter a good respiratory pump and low blood pressure are the causal agents.'

Dean gives several tracings of complete disappearance of the radial pulse for several seconds during deep inspiration. In none of the cases was the disappearance of the pulse associated with untoward symptoms.

It is noteworthy that he was dealing, with one exception, with powerful men undergoing gymnastic training, and that he noted that in certain cases posture had some influence on the result.

Watson Williams reproduces tracings of Nicholson, Mackenzie, and Dean. He also refers to a personal case of a healthy youth in whom at times complete obliteration of the radial pulse frequently occurred in deep inspiration. At other times with equally deep inspirations no obliteration of the pulse was produced. He states that in this and in similar cases he is strongly inclined to suspect that the obliteration of the pulse is due to the instrument failing to receive pulsations from the smaller (constricted) radial artery. He sums up the question by stating that 'the effect of respiration on the circulation is exceedingly complex, resulting from mechanical factors introduced by the pump action of inspiration and expiration, and from impulses generated in the bulbar cardio-inhibitory and vasomotor centres coincident with the respiration impulses; and the effects vary according to the quickness or slowness of respiration, whether it be natural or deep, or forced, obstructed or free; while the strength of the heart-beat, arterial tension, the activity of the bulbar centres, and, we may add, the action of the abdominal muscles, the splanchnic area, and even the degree of oxygenation of the blood, all have varying influences in determining the final results.

As the relative dominance of these different factors is so variable, the results as shown in pulse tracings are all inconstant.'

Lewis, as a result of a series of experiments in man and animals, came to the conclusion that in man a deep intercostal inspiration, which is not prolonged, yields a pure fall of blood pressure. A deep diaphragmatic inspiration, which is not prolonged, gives a pure rise of blood pressure. The rise in blood pressure in abdominal breathing is due to a raised intra-abdominal pressure. In expiration the reverse effects hold. He considered, therefore, that the *pulsus paradoxus* is a misnomer, as a fall in blood pressure almost always occurs when a patient is instructed to take a deep breath.

Hoke confirmed Cloetta's statement that the blood flow through the lungs was diminished during inspiration. He considers that two factors are concerned in the production of *pulsus paradoxus*: (1) the altered circulatory conditions in the lung during inspiration and expiration, (2) a hindrance to the entrance of blood either into the thorax or into the lung.

Gaisböck (*Deutsch. Archiv f. klin. Med.*, 1913, 110, 506) considers that the inspiratory diminution of the pulse is chiefly due to a stimulation by inspiration of the vasomotor centre leading to a marked peripheral vasoconstriction of the vessels.

He publishes tracings of complete inspiratory disappearance of the radial pulse in a neurasthenic youth which, in our opinion, are exactly similar to the tracings in our Cases I and II. He states that the *dorsalis pedis* became 'etwas kleiner', but did not disappear, and he gives no tracings in support of his statement. He publishes simultaneous tracings of the respiration, the arm volume, and the carotid pulse which he considers demonstrate an inspiratory diminution of the carotid pulse. As the tracing of the carotid artery was taken by means of a receiver on the neck and shows almost complete disappearance of the carotid pulse during inspiration while the *dorsalis pedis* was still palpable, the inspiratory disappearance of the carotid wave is, in our opinion, simply due to the displacement of the receiver by the muscles of the neck on deep inspiration. He describes a second case (Fall 4) in a muscular male who had accidentally discovered that his pulse disappeared on deep forced inspiration. Gaisböck found that the patient was able to abolish his radial pulse 'durch extrem forcierte andauernde Kontraktion seiner Armmuskulatur bei ruhiger, gebeugter Haltung des Arms'. As the pulse on the opposite side simultaneously showed a diminution, though to a less extent, he concluded that the phenomenon was not due directly to muscular contraction, but refers it, as in his other cases, to stimulation of the vasomotor centre. It is obvious no such movement could be carried out without forcibly fixing his scapula to his chest, and to a less extent the scapula of the other side.

We have recently had an opportunity of examining two cases of *pulsus paradoxus* in healthy adults.

Case I. Male, aged 23. A healthy medical student consulted us as he had discovered that his pulse was irregular during inspiration. He was of athletic

tendencies and presented no evidence of disease in his chest or elsewhere. When first seen it was noted that on a deep inspiration the pulse at the wrist at once disappeared and remained absent for several seconds, returning at the commencement of expiration. An attempt was at once made to trace the irregularity, the subject being in the recumbent position, but it could no longer be produced, the only effect of the deepest inspiration being a moderate sinus arrhythmia. A few days later a further attempt was made to obtain tracings of this pulse intermission. As on the previous occasion, when the pulse was first palpated with the finger, the patient standing erect, the pulse completely disappeared during deep inspiration. Attempts were then made to obtain tracings, and as it was thought that the irregularity might be influenced by the erect posture the subject was kept standing with the shoulders forward and the forearms resting on the padded back of an easy chair. In spite of repeated efforts with the deepest inspirations, no effect could be produced except a slight sinus irregularity. Later that same evening, with the subject standing in a more erect position, Fig. 1 was obtained.

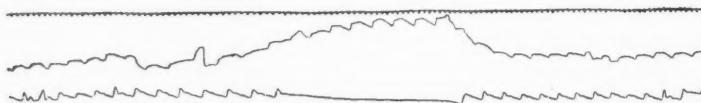


FIG. 1. Tracing from Case I. Lower tracing, radial; upper tracing, carotid. The commencement of the tracing shows a slight sinus arrhythmia. The radial pulse completely disappears on deep inspiration.

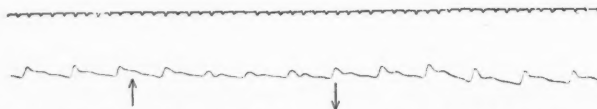


FIG. 2, Case I. Radial tracing. Slightly accentuated slow breathing. Commencement and termination of inspiration marked by ↑.

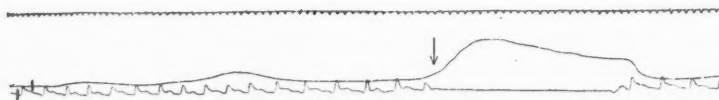


FIG. 3, Case I. First part of tracing shows normal breathing with slight sinus arrhythmia; in latter part of tracing, patient told to continue breathing as before but to retract shoulders.

The first part of the tracing shows a slight sinus arrhythmia which is of the ordinary respiratory type. On the occurrence of a deep inspiration the radial pulse completely disappears, and remains absent as long as the inspiratory position is continued. The carotid pulse continues apparently uninfluenced. Fig. 2 shows a radial tracing obtained with the subject standing in the same position during slightly accentuated respiration. During inspiration, which is marked on the tracing between the arrows, there is, in addition to a very slight sinus arrhythmia, a definite diminution in the size of the radial beats. We later discovered that the essential factor in the production of the inspiratory disappearance of the pulse was not inspiration but the position of the shoulders. In Fig. 3, the upper tracing is the respiratory curve and the lower tracing the radial. The first part of the tracing shows an ordinary slight respiratory sinus arrhythmia; at ↓ the subject was told to continue breathing as before, but in addition to

retract the shoulders. The radial pulse at once disappeared, to return immediately when the shoulders were allowed to come forward. The increased height of the respiratory tracing is not due to any increased depth of respiration, but to the fact that the respiratory tracing was obtained by a bandage round the chest at the level of the scapula.

This relationship to the position of the shoulders is constant, and in this case the disappearance of the radial pulse depends solely on the position of the shoulders, and is quite independent of the respiratory cycle or the erect posture. The deepest inspirations are, apart from a slight sinus arrhythmia, without effect on the radial pulse so long as the shoulders are kept forward, and retraction of the shoulders at once produces disappearance of the radial pulse at any stage of respiration even in the full expiratory position. By making the subject take a deep inspiration with one shoulder forward and one shoulder retracted a one-sided *pulsus paradoxus* can be obtained at will.

During the disappearance of the radial pulse the carotid, facial, and dorsalis pedis arteries, apart from the sinus arrhythmia, remain unaltered and the subclavian artery can be felt beating strongly above the clavicle, but the brachial and axillary arteries are pulseless. The subject feels no inconvenience during the longest intermissions and there is no evident interference with the venous circulation.

Case II. This subject was a healthy and athletic male, aged 24, a recent graduate, who, as he was known to have a pulse which stopped on inspiration, kindly offered himself for examination. He presented no evidence of disease in his organs and was unusually well developed. As a student he had frequently demonstrated his pulse to his fellow students and had become very expert in producing the irregularity. He produced the stoppage by holding himself very erect, bracing back his shoulders and taking a deep inspiration. Fig. 4 is a tracing from this man showing a deep maintained inspiration produced in this way. As in Case I, the radial pulse disappears on inspiration and remains absent until the onset of expiration. The facial and dorsalis pedis arteries continued uninfluenced and the subject felt no inconvenience whatever. This case differed from Case I in the fact that, although for the purpose of demonstration he generally did produce the stoppage by holding himself erect with the shoulders back, the pulse also disappeared with a free and moderately deep inspiration even when the shoulders were kept well forward. It was found, however, that if the head were kept moderately flexed upon the chest the deepest possible inspiration had no effect on the pulse. If the pulse was obliterated by a deep inspiration and inspiration maintained, moderate passive flexion of the head on the chest at once brought back the radial pulse, which again immediately disappeared on the head being passively extended to the normal position. Fig. 5 is an example of this manoeuvre. Fig. 6 is a tracing from this man showing a unilateral *pulsus paradoxus* produced during a deep inspiration with the right shoulder voluntarily retracted and the left kept forward.

We have examined a considerable number of individuals and find that in the great majority of young adult males the radial pulse at once disappears when the shoulders are voluntarily retracted, independent of respiration, although this is most easily produced by assisting the retraction of the shoulders by a full expansion of the chest. Fig. 7 is taken from a healthy male student in whom



FIG. 4, Case II. Lower tracing, radial; upper tracing, carotid. Deep maintained inspiration.



FIG. 5, Case II. Lower tracing, radial; upper tracing, respiratory curve: *a* commencement of deep maintained inspiration, *b* moderate passive flexion of head on chest, *c* passive return of head to former position, *d* cessation of inspiration.



FIG. 6. Unilateral pulsus paradoxus produced by deep inspiration with right shoulder kept voluntarily forward and left shoulder retracted. Upper tracing, left radial; lower tracing, right radial.



FIG. 7. Normal student. Upper tracing, respiratory curve; lower tracing, radial. Effect of voluntary retraction of shoulders.

deep inspiration taken in the ordinary way without special instruction has no effect on the radial pulse. When shown how to take a respiration with the shoulders back the radial pulse at once disappears. In Fig. 7 he was instructed to breathe in his usual manner and then to retract the shoulders and continue breathing as before. The upper tracing shows the respiratory curve and the lower tracing the effect of retraction of the shoulders on the radial pulse.

In females of the hospital class it is not as a rule possible to obtain disappearance of the radial pulse in this way, but it occurs in a large proportion of healthy athletic young women.

It is clear then that in such cases the inspiratory disappearance of the radial pulse is not due to any direct inspiratory effect, either from changes within the thorax or as a result of vasomotor changes, but is solely due to an indirect local action on the subclavian artery outside the thorax.

The anatomical adjustments produced in deep inspiration must be considered. The third part of the subclavian artery passes under the clavicle and the subclavius muscle. The scalenus anticus and the lower cord of the brachial plexus and the first rib lie below. On the outer border of the artery is the rib attachment of the serratus magnus. In deep inspiration the shoulder girdle is anchored to the occiput above and a pull is exerted from the shoulder girdle to the ribs by the serratus magnus and the subclavius muscle. The scalenus medius acts directly from the cervical spine. In some cases the subclavian artery may pierce the scalenus anticus muscle. In deep inspiration the first rib is approximated to the subclavius muscle under the clavicle; the muscle bellies of the subclavius, the serratus magnus, and the scalenus medius, in contracting, increase in transverse bulk; and the result of these combined adjustments is a narrowing of the exit from the subclavian triangle.

With regard to the muscular action involved in putting back the shoulders, the scapulae are approximated by the two trapezii muscles acting with the rhomboidei muscles so that the clavicle is pressed up towards the first rib. Again the result is a tightening up of the exit from the subclavian triangle.

It is difficult to imagine that any diminution so caused in the subclavian triangle could be sufficient to obliterate the pulse by circular compression which would require a pressure greater than the systolic pressure of the blood. In a recent paper, however, Hill, McQueen, and Flack have shown that by oval deformation of an artery the pulse wave can be completely obliterated with external pressures less than, and often much less than, the diastolic pressure of the blood in the artery. In a further paper the same writers have shown that oval deformation is accompanied by characteristic sounds on auscultation. In our two cases the return of the pulse on the cessation of respiration or on relaxing the shoulders was accompanied by the production of these characteristic sounds, the characters of which are fully described in the paper cited.

We conclude, therefore, that in our cases the obliteration of the radial pulse is due to oval deformation of the third part of the subclavian artery.

Fig. 8 is a typical example of the pulsus paradoxus obtained, by the courtesy of Dr. Lister, from a case of adhesive mediastinitis.

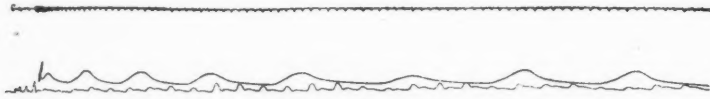


FIG. 8. Pulsus paradoxus from a case of adhesive mediastinitis. Upper tracing, respiratory curve; lower, radial tracing.

Any attempt to analyse the individual cases in the literature in pulsus paradoxus is at once faced with the difficulty that satisfactory tracings of the pulse and respiration are present in only a very limited number of the cases. It is at once evident, however, that, in addition to the ordinary vagus sinus arrhythmia, at least two entirely different conditions have been included under the term pulsus paradoxus:

1. Cases such as our Cases I and II, occurring in healthy adults, and generally presenting complete obliteration of the pulse during deep inspiration, and due in our opinion to oval deformation of the subclavian artery in the subclavian triangle.

2. Cases occurring in a great variety of conditions, in which the one common factor is an embarrassment of the circulation, and in which the normal inspiratory diminution of blood pressure exaggerated by an abnormally low blood pressure is a sufficient explanation.

It is not improbable, however, that in certain cases, especially those associated with marked dyspnoea, and cases in which the inspiratory diminution of the pulse is markedly increased by increased depth of inspiration, both types may be combined in the same case.

REFERENCES.

1. Barr, Sir James, *Brit. Med. Journ.*, 1907, i. 913.
2. Bäumlér, *Deutsch. Archiv f. klin. Med.*, 1874, xiv. 455.
3. Dean, *Journ. Roy. Army Med. Corps*, Lond., 1907, viii. 504.
4. Franck, *Gaz. Médic. de Paris*, 1878, No. 50, quoted Reichmann.
5. Gerhardt, *Berl. klin. Woch.*, 1897, xxxiv. 4, quoted Reichmann.
6. Hill, McQueen, and Flack, *Proc. Roy. Soc.*, Lond., 1914, ser. B. lxxxvii. 344.
7. Hill, McQueen, and Flack. To appear shortly.
8. Hoke, *Wien. klin. Woch.*, 1912, xxv. 998-1002.
9. Hoppe, *Deutsche Klinik*, 1854, No. 3, quoted Reichmann.
10. Kussmaul, *Berlin. klin. Woch.*, 1873, 433, 445, 461.
11. Lewis, *Journ. of Physiol.*, Camb., 1908, xxxvii. 233.
12. Reichmann, *Zeitsch. f. klin. Med.*, Berlin, 1904, liii. 112.
13. Riegel, *Berlin. klin. Woch.*, 1876, 673.
14. Riegel u. Tucek, *Berlin. klin. Woch.*, 1878, 739.
15. Riegel, *Deutsch. med. Woch.*, 1903, xxix. 345.
16. Rosenbach, *Virchow's Archiv f. Path. Anat. u. Physiol.*, Berlin, 1886, cv. 215.
17. Schreiber, *Arch. f. exp. Path. u. Pharmak.*, Leipzig, 1880, xii. 168.
18. Sommerbrodt, *Berlin. klin. Woch.*, 1877, 42 and 615.
19. Wenckebach, *Brit. Med. Journ.*, 1907, i. 63.
20. Williams, C. J. B., quoted Barr.
21. Williams, P. Watson, *Brit. Med. Journ.*, 1907, ii. 369.

PATHOLOGICAL CHANGES IN THE ADRENAL GLANDS

By T. R. ELLIOTT¹

With Plates 5-7

AN apology is needed in preface to this paper. The observations that are detailed in it do not lead to any general conclusions of obvious value; but despite that it seemed worth while to place them on record because I believe that they are made with accuracy. Many dogmatic statements on the slightest of evidence have been published with regard to excess of function of this or that part of the adrenal glands. They remain unproven, and even now there is but little to add to the clear and able summary of the subject which was written by Léon Bernard (4) in 1907.

Bernard dealt with the pathological question under three heads:

1. The relationship of the adrenal glands to other glands with internal secretions. Nothing definite, he said, is known of this; and the statement, unfortunately, is still true.

2. The reaction of the glands to infections and intoxications. French workers had observed exhaustion of adrenalin in experimental infections of animals. Bernard pointed out that these results did not make it clear that the adrenals played any essential part in the defence of the organism against infections.

3. In atheroma and hypertension he thought it proved that the renal impermeability was associated with changes in the adrenals in the direction of cortical hyperplasia, but that there was no evidence as to the nature of the lecithinogenic function of the cortex.

To physiologists the healthy gland is known as a threefold complex, of cortex, medulla, and ganglion cells. The cortex is practically a uniform tissue whose cells in the majority of animals are loaded with a special fatty substance, and often in addition with brown pigmented granules at the zone close to the medulla. Arnold's (2) old distinction of the three zones, glomerulosa, &c., is of no real value, and should be set aside. The cortical pigmented substance is a special secretory product, which appears in prodigious quantities in the gland of the guinea-pig. It and its cells may form tumours; but nothing

¹ Working in tenure of a Beit Memorial Fellowship, and aided by a grant from the Graham Research Fund, University College Hospital, London University.

is known as to its history, and I have made no special observations with regard to its presence or absence in the pathological glands described in this paper. The medulla stores up adrenalin and excretes it into the blood-stream. Sympathetic ganglion cells occur in small numbers within the medulla of the human gland, and they are always present in masses on its outside, masses which lead up directly to the main semilunar ganglion.

Recent work (10, 17) in the physiological laboratories has abundantly confirmed the first experiments of Dreyer (16) and Tscheboksaroff (44), proving that the medullary chromaffine cells are directly controlled by the splanchnic nerves, so that every strong stimulation of these nerves is attended by an outpouring of adrenalin into the circulation. Indeed, this central core of the gland is very essentially a part of the sympathetic nervous system. Its cells are not equivalent to those of ordinary peripheral glands: they belong to a higher rank, and are practically sympathetic ganglion cells which do not influence the peripheral muscle through the medium of a nervous fibre, but instead reinforce the nervous impulses of the latter by a discharge of adrenalin. Adrenalin circulating in the blood evokes from plain muscle precisely the same response, be it contraction, relaxation, or none at all, as does the sympathetic nervous impulse. Moreover, in the absence of the adrenal glands the plain muscle soon loses tone and fails to respond to the nervous call. Hence it is reasonable to think that the steady tone of all muscles innervated by sympathetic nerves depends not so much on the nervous impulse as on the influence of adrenalin circulating in the blood. To effect this result the chromaffine or 'paraganglion' cells seem to have been differentiated from the mass of the true ganglion cells, and set apart for the task of supplying this special hormone to their own department of the nervous system. The action of each is essential for perfect control: the one to hold the muscle at a uniform level of contraction in its so-called rest, and the other to effect such rapid changes, this way or that, as are needed in the quick reflex activities of the body. The relationship of the two, adrenalin and nervous impulse, may be roughly illustrated by comparing the muscle with the string of a violin, that must be screwed to its proper pitch for the fingers to play upon it and evoke the quickly changing notes.

The muscles that are especially innervated by the sympathetic are of course those of the heart and blood-vessels. They are ever at work, and life must cease if they relax their tension. It is this physiological connexion which gives such deep interest to the study of the glands, and it is this which makes it urgent to gain knowledge of their condition in the various forms of mortal disease.

If we wish, then, to know how bodily disease affects the gland, it will be necessary to consider: (1) Its structural anatomy, changes in gross bulk and in histological detail; (2) alterations in the cortical fatty substance; (3) variations in the load of adrenalin.

The Cortical Lipoid.

In healthy glands all the cells of the cortex are crammed with a curious fatty substance, and the same substance is seen in the vagrant nests of cortical cells that may be embedded in the medulla or ensheath the nerves and large veins entering the medulla. Kaiserling and Orgler (27) first pointed out that this fat is characterized by its doubly refractive properties, and that of all healthy tissues only the adrenal cortex and the cells of the corpus luteum contain anisotropic lipid, though similar substances occur frequently in the fatty degeneration of slow tissue necrosis. In a review of such fats Aschoff (3) found reason to regard them all as cholesterin esters, with which apparently lecithin² is also associated in the adrenals. Tuckett and I (20) described the distribution of this lipid in various animals in health, and showed its early loss in disease. But most writers in medical pathology have made a mistake arising from the general pathological observation that fat in an organ signifies degenerative processes, and have inferred that the cortical fat is the index of disease or altered functions of the gland. Marchetti (31) examined 1,200 post-mortem cases, believing throughout that the fat was a pathological infiltration; and Napp (34) held a similar view. This opinion is reflected in the chief text-books of medicine, so that, for example, Neusser and Wiesel's (35) monograph (1910) in Nothnagel's *Encyclopaedia* almost disregards the question of the fat. But Loeschke (30) and also Goldzieher (26) observed that the fat vanishes in all acute infections; and though E. Thomas (43) denied this to be so in children with diphtheria, scarlet fever, or measles, the statement was fully confirmed in Weltmann's (47) elaborate analysis of 600 cases. My own observations were made independently of these to continue in man what I had already seen in animals. The general features of the exhaustion in human glands were referred to in my paper with Armour (19) in 1911, and the details given in the present account agree almost identically with those of Goldzieher and of Weltmann.

Method. The glands were taken from the body as soon as possible after death, and rarely later than ten hours. They were fixed in a mixture of potassium bichromate and formalin, cut on a freezing microtome, and stained with Scharlach R. and Ehrlich's haematoxylin. Sometimes the load of fat was so abundant that the sections could hardly be submerged either in the haematoxylin dye or in water. Controls were always stained with Scharlach alone, so as to correct for loss of red tint if the sections were treated too long with the Ehrlich stain. The sections were then mounted in glycerin, either pure or

² Bernard found that lecithin formed nearly 7 per cent. of the entire weight of a horse's adrenal, and 50 per cent. of its fat. But Lapworth (29) obtained less than 1 per cent. of cholesterol and its esters in the sheep. The sheep's gland contains practically no fat that can be demonstrated under the microscope. I am not aware of any accurate analyses in the different animals which would compare in each species the amount of lipid that can be extracted chemically with the fat that is seen by histological methods.

50 per cent., and examined with the polarizing microscope.³ The doubly refractive crystals seemed to represent a more elaborate condition of the lipid than that in which it takes a deep stain with Scharlach. Indeed, a gland that is loaded to its utmost capacity in rest shows a field studded with brilliant crystals that are almost pure white or only faintly tinged with pink. It must be remembered that in life the lipid is fluid, though even then probably anisotropic, and that these permanent crystals are produced by cooling and fixation. As the load is reduced the doubly refractive crystals become smaller and fewer, while the substance stored in the cell takes a deep scarlet stain characteristic of the simpler fats (Pl. 5, Fig. 1). Finally, all vanishes and there remains only a contracted cell of a uniform blue (Fig. 2).

The path by which the lipid left the cell could not be identified. Fat was never seen in the lymphatics or blood-vessels outside the cortical cells under conditions in which post-mortem autolysis and leakage could be excluded. A cross-section of a cylinder of the cortical cells, when fully loaded, showed the nuclei to be all crowded together into the centre of the column, while the bases of the cells, adjacent to the capillary vessels, were swollen with lipid. The appearance was unlike what would be expected were secretion to be discharged into some minute lumen within the centre of the column, and it suggested the outward path along the capillaries. Still the centre of the column appeared sometimes to form a potential lumen, for it was noticed to be distended with lymph and even to contain red blood corpuscles in certain cases where thrombosis in the central vein of the medulla had caused considerable rise of pressure in the smaller vessels and so burst a way up the axis of each cylinder⁴ (Fig. 2).

The microscopic test, by Scharlach and the polariscope, revealed practically all the lipid present in the cortex. It has been proved for the liver and the heart that the appearance of fat in their cells may not mean that more fat has been added to the total bulk of these organs, but simply that fat which was always present, but was normally masked in chemical combinations that hid it from the dye, became freed to receive the stain. This was not so in the human adrenals. Dr. F. H. Thiele very kindly made for me a chemical analysis of the fat content of seven glands, and the amounts found corresponded closely with the histological picture.⁵ The Scharlach stain is therefore a reliable test for the amount of lipid in the cortex, though indeed for rough purposes even that is

³ Sections were also stained with Lorrain Smith's Nile Blue sulphate; but this method was soon discarded because the specimens could not be kept, and the distinction between acid and neutral fats, so obtained, did not appear to be of any importance.

⁴ Stoerk (42) argued against the existence of such a lumen in the heart of the cell columns, urging that in these haemorrhagic extravasations the blood lay between the cell cylinders and the enveloping connective tissue. I failed in an attempt to inject carmine gelatin into the possible lumen.

⁵ Since this was written, an admirable review of the general question by J. W. McNee has appeared in the pages of this Journal. McNee refers to an approaching paper by Landau and himself in which chemical analyses of the cholesterol in the adrenals are fully described and found to accord with the results of microscopic examination.

unnecessary. Naked-eye inspection of a cut surface of the fresh gland can at once recognize the lipid. When abundant, it gives to the tissue a yellow butter-like tint around the greyish-white medulla. In exhaustion the cortex changes from yellow to greyish brown, and is often haemorrhagic.

Apart from nodular outgrowths on the surface of the gland, cortical adenomata were occasionally seen in the medulla, where they might grow to form a considerable mass, as much as 2 cm. in diameter and forming 20 to 40 per cent. of the entire gland's weight. The cells of these were arranged in regular anastomosing columns and contained lipid like the normal cortex. But the curious feature of the real adenoma was that, despite the full blood supply, its cells parted with their lipid very slowly and were well laden even in conditions which exhausted the fat of the ordinary cortex (Pl. 6, Fig. 3). No experiments have yet succeeded in demonstrating a nervous control of the fat store in the cortical cells, like that so clearly proved for the adrenalin of the medulla. But the special behaviour of the fat in the adenomata does suggest that there may be some such machinery, and that the lipid does not disappear simply as the result of certain physico-chemical conditions of the circulating blood.

Adrenalin of Medulla.

The amount of adrenalin present in these cells can be gauged roughly in the smaller animals by the depth of the yellow-brown tint which adrenalin causes them to assume when placed in a solution of chromate salts. This chromaffine reaction is shown very well in the glands of young children, but it is unreliable in adults, so that it is quite fallacious to identify implicitly, as Parkinson (36) and others have done, the depth of stain with the amount of residual adrenalin.

For accurate work the adrenalin must be extracted from the gland, and its amount determined by quantitative methods. Mere qualitative tests, to show the presence of adrenalin in the extract by its causing a rise of blood pressure, are insufficient, because all glands, even those of Addison's disease, contain some adrenalin. For this reason the observations of Mott and Halliburton (33) on the question may be set aside; and indeed their method of dealing with the glands seems to have been in itself faulty, for they found that there was no adrenalin present in what should have been a practically normal gland, a gland taken from a woman liable to mental derangements, but otherwise healthy, who was suddenly choked by food. Quantitative assay of adrenalin in the gland extract has been attempted by several workers who used *colorimetric* methods,⁶ chiefly based on Comessatti's (15) pink reaction with mercuric chloride solution. These are in general inaccurate, failing to indicate the full amount of adrenalin.

⁶ The various colorimetric methods are fully reviewed in Borberg's paper (8 and 9). Borberg himself used the frog's enucleated eyeball, believing it to be a test of great delicacy for minimal quantities of adrenalin; but he did not measure the total amount of adrenalin in the glands of the animals which he studied in various conditions of exhaustion.

Schmorl and Ingier (40) modified the Comessatti method, and their modification increased threefold the amount of adrenalin which the test seemed to indicate. Even so the yield obtained by them as a standard of load in healthy glands was but half of what I found by my method of assay; and Goldzieher's (26) analyses, using Zanfognini's method by the reduction of manganese peroxide, show a similar deficiency. A more reliable colorimetric method does seem to have been found recently by Folin, Cannon, and Denis (22). But most of my analyses were made before the publication of Folin's method, and in consequence I have adhered throughout to my own more tedious method of intravenous injection into cats.

Method. The glands were removed with the lightest of handling as soon as possible, and often only three or four hours after death; and they were analysed absolutely at once. Dissected clean, they were weighed, and each one well ground in a mortar with sand and 80 to 100 c.c. of neutral Ringer's solution (NaCl 0.6 per cent., KCl 0.025 per cent., CaCl_2 0.025 per cent.). The mixture was rapidly brought to boiling, and filtered through glass wool. The percentage of adrenalin in the extract was determined by comparing its effects after intravenous injection on the blood pressure of a pithed cat with that of a solution of chemically prepared adrenalin of known strength. From the percentage strength was then calculated the total amount of adrenalin present in each gland, in milligrams of the base and not of the chloride.

This comparison can be made with very great accuracy, as I have shown in my paper in the *Journal of Physiology* (17), where the experimental details are given; and the figures obtained by it agree with those of Folin and Cannon to a surprising degree of closeness. The standard solution of 1:1,000 adrenalin chloride with a trace of chloroform keeps well for several weeks, and even when diluted to 1:40,000, the strength used for injection into cats, it loses only 20 per cent. in standing at room-temperature for two days. The gland extract deteriorates more rapidly, so that it must be analysed without any delay. This loss varies in different cases. For example, one extract (Case 76) fell from 3.2 to 3.0 mg. in 18 hours, a loss of 7 per cent.; while another (Case 82) fell from 1.47 to 1.0 mg., a loss of 30 per cent. in 17 hours. Fresh standard solutions were always used, and the gland extract was invariably injected as soon as it had cooled.

The main sources of error in estimating the total quantity of adrenalin residual in the gland at death must therefore lie in the loss of adrenalin during post-mortem changes of the gland, and in faults in the method of extraction. Cannon believes that a fuller yield can be obtained with an acid solvent instead of neutral Ringer. His method yielded in my hands (18) no better results than my own. Schmorl and Ingier extracted in addition to the gland all the surrounding fat, into which they thought adrenalin transuded, and consequently they were unable to determine the size and weight of the glands. This I did not find to be necessary. Still it must be conceded that the method of extraction used was probably to some extent incomplete, and that the absolute value of the adrenalin

load in the gland itself was not fully measured. The analyses were, however, always made under similar conditions, so that the values obtained at different times, and in different glands, can be justly compared with one another.

Post-mortem loss will vary with the temperature of the body and the nature of the autolytic changes, which seem to be different with different forms of death. In cats the right and left glands contain exactly equal amounts of adrenalin, and in these animals it is therefore possible to contrast the accuracy of methods of analysis, and also to determine the exhaustion of adrenalin caused by various factors. I found that an excised cat's gland kept on ice for six hours lost practically no adrenalin, whereas one kept at room-temperature ($17^{\circ}\text{C}.$) in a moist chamber for the same time lost about 30 per cent. In man the glands on each side are rarely of equal bulk, but they contain loads of adrenalin which do not differ, as a rule, by more than 0.2 mg. from one another. The difference in weight of a pair of glands is generally caused by unequal development of the cortex; and a glance through the figures given later in this paper will recognize that glands differing from one another by 0.5 gm. in weight none the less contain, as a rule, almost identical loads of adrenalin. A striking example of this equality in difference is Case 79, 7.98 gm. = 1.4 mg. and 5.63 gm. = 1.25 mg. On the other hand, a few cases do exhibit marked inequality of the adrenalin content, as Case 65, 4.88 = 2.45 mg. and 3.41 = 1.9 mg.

This inconstancy is a serious obstacle to the attempt to measure the loss of adrenalin that occurs post-mortem in man. Six cases were analysed for this purpose, and by ill fortune they chanced to have glands of very unequal size, so that the conclusions to be drawn from the analyses are of the roughest nature.

Case 71. ⁷	Gland	5 hrs. post-mortem,	4.22 grm. = 1.12 mg.	} in 5 hrs.
	" 10 "		4.38 " = 1.0 "	
" 19 a.	" 4 "	post-mortem,	6.5 " = 1.2 "	} in 8 hrs.
	" 12 "		6.44 " = 1.1 "	
" 73.	" 2 "	post-mortem,	4.27 " = 4.0 "	} in 2 hrs.
	" 4 "		5.68 " = 4.0 "	
" 82.	" 4 "	post-mortem,	4.5 " = 1.47 "	} in 17 hrs.
	" 21 "		5.92 " = 2.8 "	
" 76.	" 2 "	post-mortem,	3.1 " = 3.2 "	} in 18 hrs.
	" 20 "		4.45 " = 3.25 "	
" 72.	" 2 "	post-mortem,	2.82 " = 0.9 "	} in 20 hrs.
	" 22 "		6.65 " = 1.25 "	

Since in Cases 82 and 76 there was no demonstrable loss in eighteen hours, while the gland that was left in the body chanced to be the larger of the two and so

⁷ Two of these cases were from cerebral hemiplegia. There was no evidence of a direct cerebral control of the adrenalin load of the gland on one side rather than on the other. Sir Victor Horsley and the writer made several experiments on cats in the hope of finding a cerebral centre or tract controlling the gland of one side only, but the investigation was fruitless.

may have contained originally more adrenalin, one may suppose that the loss in eighteen hours is not more than 10 to 15 per cent.

Having thus obtained a rough indication of the loss of adrenalin that occurs in the glands post-mortem, one must next consider certain general factors that have been proved to cause rapid exhaustion of adrenalin in the few hours before death. These are much more important, insomuch as they are attended by greater exhaustion. Both the ante-mortem and the post-mortem conditions of loss in individual cases have been neglected by previous writers on this question, who have dealt rather with the relationship of the case to some particular malady. Death from disease in man is preceded by so much disturbance in mind and body that one cannot easily disentangle the separate causes in the summed effect. Consequently experiments were made to study each factor separately in animals, in which the control of the glands by the nervous system could at the same time be investigated. I found that in cats the exhaustion of adrenalin was almost entirely the result of excitant impulses passing down the splanchnic nerves, and that it could be prevented by section of these nerves. In my experiments the splanchnic nerves were cut on one side, and a week or more later the effect of the exhausting factor was determined by comparing the adrenalin loads in the resting gland on the side with cut nerves and in the other gland to which the exhausting impulses had access. Many and various were the conditions that led to loss of adrenalin, and even in a few hours this loss was very great. Emotional fright, as also shown by Cannon (10); simple anaesthesia of long duration, whether it was with ether or chloroform; excitation of afferent nerves, such as those of the great sciatic; poisoning with diphtheria toxin—all were effective, and in every case the action was through the splanchnic nerves, even in the case of diphtheria. So it was clear that the adrenal glands are played upon by the splanchnic nerves in the emotional and vasomotor reflexes with almost as frequent a call as are the muscles of the blood-vessels themselves. In such a crisis as impending death from diphtheria intoxication there is an urgent demand by the animal in its efforts to combat the fall of blood pressure and other changes due to action of the poison elsewhere. But even in diphtheria the adrenalin exhaustion is secondary, an expression of the cat's struggle for life: it is not a primary factor leading to death.

Since emotion, prolonged anaesthesia, cerebral haemorrhage with its sustained vaso-constrictor effort, and the like can rapidly exhaust the adrenalin from the gland in animals, it is evident that cases of death from disease in man, when changes in the glands are being studied, must be reviewed with close attention to the general conditions of life in the last few days, altogether apart from the special disease in question. The cases must be grouped in accordance with the main pathological disorders of the machinery of the body rather than under a catalogue of the special clinical diseases or the particular microbic infection that may be giving rise to these wider changes. In this respect the observations given in this paper have more value because, as a physician, I was personally familiar with the clinical history of the cases in which the glands were

analysed, and myself saw the post-mortem examinations. Consequently I was able to form a fair opinion of the general pathological disorders arising in the progress of each disease. In only a few examples of children with fevers were glands analysed from cases in which I had not seen the autopsies. This was material which was not readily obtained at University College Hospital, and for it I am indebted to the kindness of Dr. E. W. Goodall and of Dr. A. C. B. Biggs.

The adrenalin content was measured in eighty cases; and the cortical lipid was examined by the microscope in 170 cases. These were selected to the extent that straightforward simple cases were chosen as far as possible and complications avoided. The weights of the glands and the adrenalin load are always given separately for each gland of a pair. Most writers add the two glands together. The medulla is aggregated chiefly in a mass at the venous pole of the gland, and it rarely extends between the cortical laminae at the other pole. Adrenalin is not yielded by extraction of this cortical end, and therefore in a few cases, where fat content was required as well as adrenalin load, a small piece was cut out of the gland at this end and microscoped.

The results are described more or less separately for the cortical lipid and the adrenalin. As yet there is no physiological proof that these two substances are related to one another, and their pathological changes do not exhibit any close parallelism. The cases quoted in the next pages are classified in the first place with regard to their load of cortical lipid. To save repetition of clinical detail, the adrenalin content is given at the same time where this had been determined. But the conditions of adrenalin exhaustion are summarized in a later part of the paper.

Normal Glands.

The standard of a normal gland can only be determined by examining the glands taken soon after death from a healthy man who has died suddenly and unexpectedly, and who was subjected neither to emotional alarm nor to anaesthesia. Such material is not easy to procure on account of the delay generally caused by the necessary inquest. I examined five glands from two to seventeen hours after death. All showed a superabundant load of lipid in the cortex, the substance being so rich that it did not stain deeply with Scharlach but gave a glittering field of light through the crossed polarizing prisms. Two of these were taken from healthy men killed in railway accidents.

Case 1. Man, aged 44. Cervical spine crushed by railway engine as he was going to work in the morning after a full night's rest: death was instantaneous.

Adrenal glands analysed six hours post-mortem,

4.1 gm. containing 4.0 mg. adrenalin.

3.85 gm. containing 4.1 mg. adrenalin.

Two others were from ruptured aneurisms, in cases which were in good general health and had no septic fever; and the fifth was from a man with

a small tuberculous lesion in the lung, who had been progressing most favourably without fever or loss of weight, but who died in a few minutes from a profuse haemoptysis.

Case 2. Man, aged 48. Aneurism pressing on bronchus and oesophagus; no fever and no pain. Rupture into oesophagus and speedy death.

Glands 17 hrs. post-mortem, 3.72 grm. = 5.0 mg. adrenalin.

3.74 grm. for microscope.

Each normal gland of an adult in fair health should weigh about 4 grm., and contain from 4 to 5 mg. adrenalin:⁸ the cortex should be loaded with doubly refractive lipid throughout. Schmorl and Ingier found an average yield of only 2.35 mg. for each gland in fifteen normal cases, which illustrates the insufficiency of their method of analysis.

Starvation.

Slow inanition leads to emaciation and complete loss of body fat. The cortical lipid is in nowise reduced in this process. Its storage and its loss are determined by conditions altogether different from those controlling the general fat dépôts of the body. As will be seen later, septic infections cause it quickly to vanish, whereas simple conditions of bodily emaciation leave it totally unaffected.

Case 3. Girl, aged 17. Died in six months of anorexia nervosa, she having apparently assumed this hysterical state by imitation of a sister. No fever. Body wasted almost to a fleshless skeleton, weight 3 st. 6 lb.; no lesions found post-mortem. Adrenals crammed with lipid to extreme degree; adrenalin not measured.

Case 4. Woman, aged 29. Died in eight months of anorexia nervosa. Body so wasted that no fat was seen anywhere post-mortem; ordinary height, and weight 3 st. 10 lb. In the last week there was slight fever from gangrenous broncho-pneumonia, and this must have tended to reduce the lipid and the adrenalin, and to increase the weight of the glands, which were otherwise normal.

Glands 14 hrs. post-mortem, 5.82 grm. = 2.0 mg.

5.2 grm. = 2.0 mg.

Fat plentiful, but already escaping from the cells by early autolysis. The fat in the corpora lutea was full and normal.

Case 5. Man, aged 39. Dysentery and ulcerative colitis for years; very emaciated and feeble. Died of incessant diarrhoea, without fever. All organs shrunken, and heart weighed only 6 oz. (170 grm.).

Glands 10 hrs. post-mortem, full of doubly refractive fat.

4.8 grm. = 1.8 mg. adrenalin.

Case 6. Child, aged 8 weeks. Death by inanition from hypertrophic pyloric stenosis. Glands filled with doubly refractive fat.

⁸ This 1:1,000 proportion of adrenalin to the weight of the entire gland, cortex as well as medulla, oddly holds good also for the cat—average for each gland 0.2 grm. with 0.22 mg. adrenalin—and even for cattle. Parke Davis & Co. informed me that 1 kilogram of slaughter-house glands are needed to yield 1 grm. of pure adrenalin.

Similarly in thin diabetics and in cancer of the stomach, where the emaciation is extreme, the load of cortical lipid is none the less full.

In this reference may be quoted Federici's (21) observations that there is no change in the cortical fat of bats or dormice relative to the state of hibernation; and further, that starvation to death does not alter the fat of a guinea-pig's gland.

Simple Heart Failure.

Broadly, death by heart failure, when it is not caused by disease elsewhere in the body, may occur in one of three forms:

(a) Sudden stoppage of the heart, that is presumably by ventricular fibrillation. Cases of pulmonary embolism or auricular thrombosis are not essentially faults of the heart.

(b) Rapid dilatation and failure of the heart, associated with a pulsating liver and some cyanosis, but often only slight dropsy. The patient dies in a few days, and may suffer much mental distress in the acuteness of the collapse.

(c) Progressive failure of the circulation with general water-logging and an apathetic death by slow degrees.

Three cases of (a) were examined from patients with mitral stenosis and auricular fibrillation, and one from aortic regurgitation. The glands had their normal load of lipid and of adrenalin. On account of the emotional distress and the effort made by the patient to restore the fast-failing circulation, (b) might be expected to reveal some demand on the adrenal glands. Only two examples were analysed and in them the lipid was almost normal, but the adrenalin was much reduced.

Case 7. Girl, aged 16. Aortic and mitral disease of old rheumatic origin. Attack of purpura three weeks before death, followed by fatty degeneration of the heart and complete breakdown in last week: final acute collapse with great distress in last thirty hours, subnormal temperature and imperceptible pulse.

Glands 9 hrs. post-mortem, fairly loaded with lipid.

4.35 grm. = 0.7 mg. adrenalin.

Case 8. Woman, aged 26. Ill for three years with mitral regurgitation from an hypertrophied feeble heart (23 oz. = 650 grm.). Blood pressure never raised. Complete failure in last few days with oedema, cyanosis, cold sweat, feeble though regular pulse (120) and much mental distress. No valvular lesion found. No atheroma: kidney normal.

Gland 8 hrs. post-mortem, 4.7 grm. = 0.2 mg.

Other gland of same size and full of lipid.

(c) gave variable results in the five cases examined, but the lipid was often in part exhausted, and there was generally a round-celled infiltration of the gland.

Case 9. Man, aged 35. Mitral stenosis and auricular fibrillation. Very slowly his circulation became impeded by thrombosis within the dilated auricles. The left auricle was distended with clot, which spread into the lungs causing extensive infarction for at least a week before death. No mental distress. The patient was semi-comatose, with a very cold skin, for the last two days. Kidneys

only congested. Aorta small and free from atheroma, but pulmonary arteries very atheromatous from old-standing obstruction.

Glands 2 hrs. post-mortem, fat normal. Weight increased by slightly haemorrhagic congestion.

$$5.42 = 2.3 \text{ mg.}$$

$$5.78 = 2.3 \text{ mg.}$$

More cases need analysis under this last grouping, but the main result is clear, that simple cardiac failure is not associated with loss of lipoid, though it may be with exhaustion of adrenalin, where the patient has been fighting hard for life.

Pneumonia.

Of this disease eight adult cases were examined. Three were acute, with death in three days; and they showed the most marked changes of all the glands that were ever examined. They were utterly exhausted of lipoid, and much enlarged by general oedema.

Case 10. Man, aged 37. Pneumonia for three days. Temperature 101°. Lungs, soft purple consolidation.

Glands 5 hrs. post-mortem, 11.6 gm.

$$10.35 \text{ gm.} = 1.45 \text{ mg. adrenalin.}$$

Lipoid completely gone, and the cortical cells looked very small, as though they were compressed by the general oedema of the tissues. The glands were twice their normal size.

In more prolonged cases of pneumonia the oedematous enlargement and the exhaustion of lipoid were less, even though death came with cyanosis and the rapid pulse of heart failure. For example, three patients who survived to the seventh or tenth day had glands which weighed 6 and 7 gm. each, and contained a little fat.

Case 11. Man, aged 42. Pneumonia of right side, seven days. Toxic collapse with strain of being brought to hospital.

Glands 22 hrs. post-mortem, fat almost gone.

$$7.4 \text{ gm.} = 1.2 \text{ mg. adrenalin.}$$

Case 12. Man, aged 39. Right lung, eight days. Temperature 104°. Grey cyanosis.

Glands 10 hrs. post-mortem, 6.0 gm., very little fat.

$$6.7 \text{ gm.}$$

Case 13. Man, aged 42. Pneumonia complicating syphilitic aortic regurgitation. Ill six days. Heart 23 oz. Evidence in liver of slight chronic heart failure. Pneumonia both bases.

Glands 4 hrs. post-mortem, swollen, and only a little fat in inner zone.

$$7.23 \text{ gm.} = 2.5 \text{ mg.}$$

$$6.72 \text{ gm.} = 2.5 \text{ mg.}$$

But in two cases, aged 50 and 67, of the so-called 'asthenic' type, which lived twelve days and showed practically no rise of temperature at all, though the lungs were consolidated with a puriform exudate, the glands were of normal size and contained a fair amount of fat.

Similarly in a woman of 36, who shortly after induction for placenta praevia died with bronchitis and cyanosis that developed to the fatal issue in four days but was not accompanied by a temperature above 99°, while there was neither pneumonia nor uterine sepsis, the glands had a tolerable load of lipoid. In this last example, such loss of fat as had occurred in the last two or three days of life was prettily shown, because venous thrombosis had occurred before death at one pole of the gland and in this area, in which degenerative changes had not had time to take place, the accumulated lipoid was richer and more anisotropic than in the rest of the gland.

Of children, aged from 7 months to 2 years, five examples were studied, with pneumococcal infection of lungs, pleura, meninges, or peritoneum. All showed considerable exhaustion, fat being left only in the thin outer rim of the gland.

Acute Fevers.

Measles (two cases) and scarlet fever (three cases) showed rapid exhaustion of fat in the acutely fatal cases, just as in pneumonia: scarlet fever is distinguished by a special round-celled infiltration through the gland. The glands are exhausted in young children much as in adults, but in them there is a marked tendency for the fat to cling longest to the outer rim, the zona glomerulosa; that is, to the outer rim of the true cortex, not to the entire ring of true cortex enclosing the degenerating foetal tissue (19), for this latter has all disappeared at the age of one year, and is indeed very small at the age of six months. E. Thomas (43) stated that there was no loss of cortical fat in children with measles or scarlet fever, and in that he was certainly wrong. Weltmann (47) thought that the exhaustion, though quite evident, was less readily produced in children than in adults. I have seen no reason to assent to this opinion, except in regard to the thin outer fat-holding rim.

In very young children it is interesting to compare the behaviour of the true cortical lipoid with that of the degenerating fat. The latter is present in the dying cells of the central remnant of the foetal cortex. With bronchopneumonia, gastroenteritis, or any other such febrile cause of death, the cells of the true cortex are exhausted of lipoid; but the degenerative fat of the inner area shows no change, although there is full circulation in the capillaries around it.

Diphtheria does not produce the same change as scarlet fever or measles. It is a disease of great toxicity, but little pyrexia; and it is not attended by marked loss of lipoid. Three cases were those of death associated, so to speak, with the accidents of diphtheria. The first (1½ years old) was a laryngeal diphtheria with death on the second day by haemorrhage during an attempted tracheotomy: the glands were absolutely normal and loaded with doubly refractive lipoid. The second, in a child of 5, was again laryngeal, with death on the third day by simple asphyxia: once more the lipoid was almost normal. Lastly was a case of post-diphtheritic neuritis.

Case 14. Child aged 2 years and 8 months. Faucial and laryngeal diphtheria. Good recovery, and then death on thirty-fifth day with asphyxia and early broncho-pneumonia after two days' paralysis of diaphragm.

Glands 4 hrs. post-mortem, fat full.

1.56 grm. = 0.7 mg. adrenalin.

Thus in these simple asphyxial deaths the lipid was present in abundance, and in the first two it was unaffected by the slight diphtheria poisoning of the body.

In contrast with them were three cases of the extremely toxic type of haemorrhagic diphtheria, aged from $3\frac{1}{2}$ to 6 years, and dying from the fourth to the eighth day. Here the cortical lipid was moderately exhausted, very much less so than in scarlet fever or pneumonia. Still, there was some exhaustion, so that the cortical cells were taking only a blue stain at the very time when the kidneys and heart were stained red with fatty degeneration.

Case 15. Child, aged $3\frac{1}{2}$ years. Haemorrhagic naso-pharyngeal diphtheria. Ill two days. Pulseless when admitted to hospital and died one hour later. Superficial and deep haemorrhages.

Glands 17 hrs. post-mortem, fat fair.

1.4 grm. = 0.37 mg. adrenalin.

To complete the account of the children, details may be given here of the conditions of marasmus to which reference has already been made. In four cases of gastro-enteritis, which lived from five to twenty-one days and all displayed fever until the final collapse, the fat was lost from the true cortex.

Case 16. Child, aged 2 years and 8 months. Diarrhoea for one week following bronchitis. Temperature 101° .

Glands 12 hrs. post-mortem, 1.71 grm. fat lost.

1.62 grm. = 0.31 mg.

Case 17. Child, aged 1 year and 2 months. Diarrhoea and vomiting for three weeks and slight bronchitis.

Glands 5 hrs. post-mortem, a little fat only in outer rim.

On the other hand, in three children which died in the first year from wasting without fever or any ascertainable cause, and in one case of hypertrophic pyloric stenosis (6), the cortex contained a considerable amount of lipid.

Various Septic Conditions.

Seven cases were examined, and all showed much exhaustion of lipid, whether the disease were brief or of long duration. Thus an influenzal septicaemia with fever of 98° to 102° for two months in an old man of 74, and a staphylococcal pyaemia of five months, had both utterly fatless glands.

Case 18. Man, aged 29. Staphylococcal pyaemia for five months, and perinephritic abscesses developing from foci in kidney. Continuous fever and very emaciated.

Glands 20 hrs. post-mortem, no fat, but rather oedematous.

7.72 grm. = 2.5 mg. adrenalin.

A chronic meningitis of five weeks, and another of three days, both with fever, were equally exhausted of all lipid.

Case 19. Boy, aged 13. Chronic septic meningitis from middle ear. Fever to 103°.

Glands 5 hrs. post-mortem, fat exhausted.

4.75 grm. = 2.0 mg. adrenalin.

But two milder cases, a chronic empyema and an actinomycosis of the chest, showed incomplete exhaustion.

Case 19a. Fully grown girl, aged 16. Suppurative meningitis from otorrhoea, five to six days: fever 103°. Glands oedematous, but not haemorrhagic; fat largely exhausted.

Right, 4 hrs. post-mortem, 6.5 grm. = 1.2 mg. adrenalin.

Left, 12 hrs. post-mortem, 6.44 grm. = 1.2 mg.

Malignant Endocarditis.

This disease combines heart failure with toxic septicaemia and prolonged fever: the first factor has been shown to have only slight influence, if any, on the cortical lipid, whereas septic fever in general causes exhaustion. Six cases were examined, and the lipid exhaustion was well marked in all, though never so complete as in pneumonia, nor were the glands oedematous and enlarged as in the latter disease. Two of the cases had repeated rigors, dying after illnesses of only eight and twelve weeks and presenting the clinical appearance of profound sepsis; yet there was a little lipid to be found in each under the microscope. A rapid streptococcal case, with death in five weeks, was the most exhausted of all.

Case 20. Woman, aged 37. Ill twelve weeks with very septic infection of aortic valves. Temperature 103°, and rigors.

Glands 13 hrs. post-mortem, fat largely exhausted.

6.47 grm. = 2.1 mg. adrenalin.

Case 21. Woman, aged 57. Mild septicaemia for ten weeks with fever 99° to 100°.

Glands 8 hrs. post-mortem, fat moderately exhausted.

3.72 grm. = 2.3 mg. adrenalin.

Case 22. Woman, aged 22. Mild endocarditis for five months, and uraemic death by toxic nephritis and dropsy with fever.

Glands 20 hrs. post-mortem, fat fair; a little oedematous.

6.3 grm. = 0.75 mg. adrenalin.

4.7 grm. = 0.35 mg. „

Case 23. Woman, aged 23. Ill six months with continual fever. Temperature 102°.

Glands 8 hrs. post-mortem, 5.39 grm. = 0.75 mg.

5.37 grm., fat only in small areas.

Though rarely complete, the loss of yellow fat from the cortex was always so manifest to the naked eye that this change in the adrenals at an autopsy is as valuable a suggestion of the septic nature of a doubtful case of endocarditis as is an enlarged spleen, for the glands from death in ordinary heart failure carry an abundant load of lipid.

Nervous Diseases.

In the simple cases of death from damage of vital nervous centres, whether it be the heart or the respiration that fails, there is naturally no exhaustion of the lipoid. Thus a girl of 18 died with an afebrile ascending myelitis of the spinal cord, respiration being paralysed on the ninth day: the glands showed normal fat and a full chromaffine yellow.

Case 24. Man, aged 52. Subacute combined degeneration of the spinal cord for ten months. Rapid collapse and death by heart failure in twenty-four hours, presumably by the development of a bulbar focus of myelitis. No fever.

Glands 5 hrs. post-mortem, 5.57 grm., with fair load of lipoid.
4.9 grm.

Case 25. Man, aged 55. Pachymeningitis haemorrhagica on left side, with headache for ten and coma for two days. Slight fever on last day. Kidneys normal.

Glands 6 hrs. post-mortem, 4.95 grm. = 3 mg.
4.85 grm., and very full of fat, giving on chemical analysis the highest percentage of all examined.

Carcinoma.

Death comes in so many ways to the victims of cancer, that it serves but little purpose to collect many examples under this heading. In simple cases, where there was no outspoken secondary sepsis and the patient succumbed rather to inanition, the glands were always well loaded with lipoid and with chromaffine substance. Thus in three subjects of cancer of the stomach, with death by vomiting and extreme emaciation, the adrenals were full of fat. Secondary deposits were very frequent in the glands, occurring in the first place in the medulla. As these spread outward into the cortex, their compression of the nearest cortical cell columns checked mechanically the formation and storage of fat by the latter, which therefore took only a blue stain close to the growth. In several sections the growth in the cortex seemed to be lying within the heart of the cortical cell columns, distending the potential lumen that was described earlier as being engorged with blood in glands where the central vein was thrombosed.

Case 26. Woman, aged 42. Cancer of lungs with outgrowths causing pleural and pericardial effusions. Ill four months. Sudden death by pulmonary embolism, during quiescent period after slight fever.

Glands 18 hrs. post-mortem, full of lipoid.
6.32 grm. = 4.2 mg.

This was practically a case of sudden death in a cancerous patient, and it illustrates well the fact that the glands are not affected by the simple growth of cancer in the body.

The next case, in which a man died in slow asphyxia with great cyanosis and dyspnoea but no fever, proves, together with Case 14 of diphtheritic laryngitis, that asphyxia does not affect the lipoid of the cortex.

Case 27. Man, aged 44. Sarcoma of thyroid with very large and numerous secondary deposits in the lungs, causing a slow asphyxial death. No fever. Glands 11 hrs. post-mortem, well filled with doubly refractive lipid.

Tuberculosis.

In view of what has been recorded for other fatal diseases it would be natural to expect that acute tuberculosis with high fever, or tuberculosis complicated by secondary septic infections, would be especially associated with loss of cortical lipid; and that the more chronic tuberculous changes, however great the bodily emaciation produced, would lead to less exhaustion. Such was found to be the case in the nineteen examples of this infection.

Case 28. Man, aged 45. Pulmonary tuberculosis eighteen months, with rapid development at end and persistent fever, 99° to 102°.

Glands 11 hrs. post-mortem, normal size. Fat quite exhausted.

Case 29. Woman, aged 36. Old tubercle at apex, which spread and caused rapid death by miliary tuberculosis of both lungs eight days after confinement at sixth month. No fat in lutein cells of ovary.

Glands 22 hrs. post-mortem, 5.4 grm., very little fat.
5.81 grm.

Case 30. Boy, aged 12. Miliary tuberculosis of lungs, liver, spleen, kidneys, and brain. Persistent fever, so that it was mistaken for some time as typhoid.

Glands, a very little fat in outer rim.

Case 31. Child, aged 1 year. Miliary tuberculosis and meningitis: two weeks' fever to 100°.

Glands 5 hrs. post-mortem, a little fat only in outer rim.

Case 32. Woman, aged 45. Tuberculosis of lungs and intestines: three weeks' fever 100° to 102°, and terminally enteritis and laryngeal dyspnoea.

Glands 8 hrs. post-mortem, oedematous and a little scattered fat.
8.8 grm. = 2.14 mg.

Case 33. Man, aged 28. Miliary tuberculosis of lungs and meninges, resembling typhoid. Temperature 100°. Death in three weeks.

Glands 24 hrs. post-mortem, 7.05 grm., fat fair.
7.8 grm. = 1.4 mg.

The damage of the glands in Addison's disease is a familiar statement in pathology, both cortex and medulla being destroyed by the fibro-caseous inflammation. So little cortex is left at the time of death, that one might fairly argue that the cortex as well as the medulla must be destroyed before the illness puts an end to life. The process is chronic and afebrile; and in the few cortical cells that may chance to escape the general inflammation fat can still be detected, just as there may be still a trace of adrenalin in the gland. But in some rapid cases, where the adrenals are infected and destroyed in the course of a generalized active tuberculosis, there is fever and the few surviving cortical cells are empty of fat.

Case 34. Man, aged 25. Addison's disease for six months. No fever. Slow death by general weakness. No active tubercle elsewhere.

Glands 6 hrs. post-mortem, enlarged and fibro-caseous; no medulla left; the few cortical cells that had escaped still stained brilliantly with Scharlach (Fig. 4).

Case 35. Man, aged 29. Old, healed tuberculous caries of spine. Addison's disease for rather less than a year. No fever, and no tubercle elsewhere.

Glands 7 hrs. post-mortem, enlarged, caseous and cretaceous.
10.1 grm. = 0.03 mg.

Case 36. Man, aged 34. Chronic Addison's disease for ten years. Developed pulmonary phthisis and died in two months, the temperature being always subnormal despite the disease in the lungs. Adrenals of extremely atrophic type, so that they could not be dissected out and weighed. No accessories discovered.

Glands 6 hrs. post-mortem, one side assayed for adrenalin = 0. Other side: a few giant cell systems and areas of inflammation. No medulla seen. Ganglion cells normal. Few clumps of cells, containing brown pigment but no fat, being apparently cortical.

Case 37. Man, aged 51. General tuberculosis for some months. Fever 99° to 100°. Weakness and pigmentation in last few weeks. Old tuberculosis of mesenteric glands; miliary tuberculosis of lungs, liver, and kidneys.

Glands 4 hrs. post-mortem, shape preserved, but only a few nodules of live cortical cells seen at the periphery, and from these the lipoid was gone. Much of the cortex showed its normal columnar structure and was free from tuberculous inflammation; but its cells were necrosed, either from recent tuberculous poisoning or from vascular obstruction.

Anaemia.

Up to this point all the fatal maladies, which have been discussed in this paper and shown to be associated with loss of the cortical lipoid, have had one feature common to them, namely, rise of temperature. This section introduces a fresh group. Eight cases were examined of death by haemorrhage from gastric ulcers, either acute or chronic. In all of these death was the result of repeated haemorrhage extending over several days, and in the last two or three days there was generally mild delirium with slight fever. The heart and the liver often showed degenerative increase of fat under the microscope, but the lipoid load was definitely reduced in all the adrenals, though never to complete exhaustion. This was the result, whether the temperature had been febrile or normal. The glands were a little heavier than normal, averaging 6 grm. each.

Case 38. Man, aged 30. Chronic duodenal ulcer with symptoms for eighteen months. Death by haemorrhage recurrent for twenty days, with mild delirium in last three days. Temperature 98° to 99°. Pulse 120. Saline infusions were used freely, so that at death the body contained a fair amount of blood. Kidneys normal, and their veins not thrombosed.

Glands 1½ hrs. post-mortem, fat exhausted, and recent haemorrhage on both sides at cortico-medullary zone, so that the glands were much enlarged. Neither cortex nor medulla was actually ploughed up, but the effused blood lay in a large clot between them. Fair chromaffine yellow.

Case 39. Man, aged 50. Chronic gastric ulcer with pain for five months and haemorrhage; very anaemic. Heart showed 'tabby cat' striae of fatty degeneration.

Glands, fat largely exhausted, but chromaffine a good yellow.

Case 40. Woman, aged 69. Recurrent haemorrhage for two weeks from two acute gastric ulcers. No fever. Delirium in last two days. Fibrosed kidneys.

Glands, fat practically exhausted; large cortical adenomata.

The next instance (Case 41) was complicated by a mild septic endocarditis, which may by its toxic influence have caused the fresh bleeding from the chronic ulcer: death seemed to be due to the haemorrhage rather than to the septicaemia.

Case 41. Woman, aged 33. Chronic gastric ulcer with haemorrhage for ten days, and mild delirium for three days; fever of 102°. Recent tricuspid endocarditis and septic spleen.

Glands 7 hrs. post-mortem, 5.05 grm., very little fat left.

6.7 grm. = 3.25 mg.

Two other cases, in contrast with those already quoted, showed a moderate load of lipoid and a fair chromaffine yellow. One was from an acute ulcer, where a slight bleeding was eight days later succeeded by a big haemorrhage, that continued and was fatal in a few hours; and the second was a chronic gastric ulcer that bled repeatedly for sixteen days while the patient, a man of 51, was heavily drugged with morphia and atropin (T. 99° to 100°. Gland 6.45 grm., with a fair load of fat).

Similar to these two was a clear case of splenic anaemia with death from repeated haemorrhages and terminal thromboses in the portal veins; and in this, too, there was no loss of fat.

Case 42. Man, aged 30. Repeated haematemesis and melaena for last eight months of life. Spleen much enlarged. Liver unchanged. No ascites. Blood extremely watery. Mild delirium in last three days. Thrombosis of superior mesenteric veins.

Glands 8 hrs. post-mortem, abundant lipoid.

4.26 grm. = 2.5 mg.

The group of anaemias from haemorrhage is, therefore, one which behaves inconstantly. In many cases the fat is exhausted; in others it shows no change. The factor which determined this difference could not be recognized.

Leukaemia.

The condition in this malady is complex. There is the tumour-like overgrowth of the leucocytes, whether floating or massed in various organs: there is often fever and secondary anaemia. The last two factors in themselves have a definite exhausting influence on the cortical lipoid; though it must be noted that the fevers, which so far have been shown to be associated with exhaustion, were of external septic origin, and not caused by intrinsic changes in the body itself, as seems to be the case with the febrile phases of leukaemia.

Only five examples were analysed. Four were acute cases, accompanied by fever and resulting in death within six months. Of these one was a child of 4½

years, which practically bled to death from purpura of the alimentary canal; the other three were adults, two lymphatic and one spleno-medullary. In all, the adrenals were largely exhausted of lipoid, though, as in the secondary anaemias, fat might appear in excess in the liver and heart. The adrenal glands were in no case enlarged, for, though lymphocytes were present in their capillaries, they did not lodge within the gland and form germinating areas as in the kidney or liver.

On the other hand, a very chronic case of lymphatic leukaemia in an old man of 69, with a high leucocyte count of 500,000 cells to the c.mm., showed very slight loss of lipoid. This example, however, was complicated by an opposing factor, fibrosed kidneys with high blood pressure, so that it is hardly worth quoting in this respect.

Post-operative Shock and Death.

It serves no purpose to summarize the different views that are held with regard to the nature of 'shock' as the cause of death following an extensive operation. My observations on cats proved that a long anaesthesia, or stimulation of afferent nerves, can each exhaust adrenalin from the gland, but the lipoid was not found to be much changed under such conditions. In five cases in man where a prolonged operation was followed by shock and death within twelve hours, the lipoid was present in abundance, and there was only moderate reduction in the load of adrenalin.

Case 43. Man, aged 57. Tongue excised for cancer. One week afterwards the glands of the neck were removed in an extensive dissection of three hours under intravenous ether. The patient died $1\frac{1}{2}$ hours later of heart failure.

Glands 5 hrs. post-mortem, most abundant lipoid. 3.59 grm. = 3.6 mg.
3.7 grm. = 3.6 mg.

Case 44. Woman, aged 47. Wertheim's operation for cancer of uterus. Thirteen days later the vagina was removed under intravenous ether. The operation lasted forty-five minutes, but the patient never rallied and died eight hours afterwards. No fever.

Glands 8 hrs. post-mortem, 4.4 grm., fat most abundant.
4.76 grm. = 3.2 mg.

Case 45. Woman, aged 38. Optic neuritis, which was probably due to renal disease without high blood pressure or other manifest features, led to mistaken diagnosis of cerebellar tumour. Occipital decompression under open ether, $1\frac{1}{2}$ hrs. Dura not opened, but patient lost much blood and became pulseless during the operation: she remained comatose and died fifteen hours later with a final temperature of 107° .

Glands 12 hrs. post-mortem fat abundant.
3.63 grm. = 1.5 mg.

Case 46. Girl, aged 13, in good health. Plastic operation for two hours under chloroform to restore contour of face, which had been disfigured by scars of old cancrum oris. Death as soon as patient left the operating theatre, from a blood clot in the trachea. Before the operation temperature, pulse, and respiration were normal, so that the patient was probably free from anxiety.

Glands 18 hrs. post-mortem, fat irregular.
2.65 grm. = 1.8 mg.

These examples prove that an anaesthetic leaves the lipid almost unchanged, and Case 45 shows further the important point that a rapid non-septic rise of temperature to 107° also does not cause it to vanish.

Ductless Gland Disease.

These diseases are thrown together in reference to the prevailing theory that the ductless glands form a mutually dependent ring, in which damage of one is bound to affect the activities of the rest and lead to the phenomena of 'pluriglandular insufficiency'.

Diabetes, with death by coma, supplied five cases. Of these three were extremely emaciated, while two were better nourished, but succumbed to secondary infections in the lungs. The adrenals were simply normal in size and they contained a fair load of lipid except in the two cases of secondary infection, so that the loss in the latter was evidently related to the septic state and not to the diabetes or emaciation.

No tendency to an increase of the cortical lipid, like that in kidney disease, was observed; though Klinkert (28), using Windaus's digitonin method of analysis, found a definite increase of the cholesterin in the blood in cases of diabetes mellitus with acidosis (0.38 per cent. instead of the normal 0.17 per cent.).

Case 47. Woman, aged 35. Diabetes for one year and coma for thirty-six hours. Not emaciated.

Glands 20 hrs. post-mortem, fat fair load.

4.53 grm., medulla very small.

Case 48. Woman, aged 25. Diabetes about six months, bronchitis and tuberculosis. Temperature only 97°. Very wasted. Pancreas not fibrosed, and cause of diabetes doubtful.

Glands 23 hrs. post-mortem, fat moderately abundant, but not in anisotropic form.

Case 49. Man, aged 28. Diabetes one year, tuberculosis and pyoneumothorax for four months, but only slight pyrexia. Very thin. Pancreas fibrosed.

Glands 18 hrs. post-mortem, fat, moderately exhausted.

Case 50. Man, aged 62. Diabetes and gangrene of foot with coma. Body well nourished and reeking of acetone.

Glands 8 hrs. post-mortem, yet remarkably autolysed.

Fat very abundant. 6.8 grm. = 2 mg.

Pituitary disease furnished only one example, and this did show pluriglandular changes. Acromegaly had developed ten years earlier. Ultimately some features of subpituitarism appeared as the gland enlarged into a sarcoma-like growth that compressed the frontal lobes. The thyroid grew bigger and cystic degeneration within its substance became so extensive as to cause difficulty of breathing. The adrenals were enlarged.

Case 51. Man, aged 41. Acromegaly for ten years, and latterly patient became blind in one eye and rather obese, while the symptoms of an intra-

cranial tumour declared themselves. The thyroid was so enlarged by colloid cysts in the last two years, that hemithyroidectomy was first performed for the dyspnoea. Later an attempt was made to explore the pituitary fossa by intranasal operation. This took three hours under chloroform and did not cause great shock, but the patient died suddenly an hour later by asphyxia from blood in the windpipe.

Glands 15 hrs. post-mortem, 7.83 grm. = 4.2 mg.
6.0 grm. + a lost fragment; moderate load of lipoid.

Perhaps there was not enough evidence for regarding the ultimate condition of the man as that of subpituitarism, for his obesity might have been simply the result of the sedentary life⁹ imposed by his blindness. But the pituitary¹⁰ was at any rate changed, and with this was undeniable overgrowth of the thyroid and of the adrenals. The latter seemed to be symmetrically enlarged, but the adrenalin load was not much increased, if one may argue from Cases 43, 44, and 46 that the loss under the anaesthetic and the operation had probably not exceeded 1 mg.

Reinhardt and Creutzfeldt (39) mention hypertrophy of the adrenals in a case of acromegaly, but they do not support the statement by giving the weight of the glands.

In *thyroid* disease the evidence was uncertain, though it suggested enlargement of the adrenals. A child that was born two weeks prematurely from a mother with pronounced exophthalmic goitre and itself displayed the disease (48) died on the second day from cerebral haemorrhage caused in delivery. Its glands were normal, 2.42 and 2.23 grm., but the paraganglion aorticum was a little enlarged. A woman of 23, with exophthalmic goitre, who died during an operation for removal of part of the gland, had adrenals with a normal amount of fat and slightly increased weight, 5.2 and 6.1 grm. And a third example was in a woman of 29, with acute enlargement of the thyroid in the last three months of pregnancy, but no obvious phenomena of exophthalmic goitre. She died three days after confinement in a state of asphyxia; and while one gland weighed 5.5 grm., the other was increased by a large central adenoma of the cortex to 9.3 grm. Such adenomata may, however, occur in any condition of health or disease. The lipoid in both was practically normal. In none of these was the adrenalin load measured.

Case 51a. Woman, aged 28. Exophthalmic goitre with dyspnoea and tachycardia for 4 months. Vomiting developed and was fatal in 4 days; pulse 180; no fever. Pituitary, 0.53 grm., and containing no colloid.

Glands slightly oedematous; no adenomata; fat almost exhausted.
24 hrs. post-mortem, 6 grm. = 2.5 mg. adrenalin.
5.75 grm. = 2.5. mg.

⁹ I have seen a man whose weight increased from 13 to 17 stones in eighteen months after the excision of one adrenal gland, but the corpulence in this case was almost certainly caused by his having taken up an indolent occupation.

¹⁰ A 20 per cent. extract of the tumour contained no pressor substance of the type of pituitary extract.

Finally, one may mention at the end of this section an irrelevant case of pure toxæmia of pregnancy.

Case 52. Woman, aged 30. Confinement at full time; albuminuria, jaundice, and coma, without fits, at once set in, and culminated in death 48 hours after the birth of the child. Liver necrosed.

Glands normal size; no thrombosis or necrosis; outer half fully loaded with lipoid.

Kidney Disease.

The relationship of kidney disease to changes in the adrenal glands, both in the cortex and medulla, has been the subject of much theoretical discussion. This will be considered later on (pp. 82 to 87), and here only the simple facts are narrated as regards the cortical lipoid.

Patients with renal disease, in addition to dropsy, high blood pressure, and uræmic intoxication, may suffer with secondary infections. The latter condition in itself is likely to exhaust the lipoid, and therefore examples must be taken first where death is the direct result of the kidney mischief.

A. Contracted kidneys with high blood pressure.

Case 53. Man, aged 51. Small, fibrosed red kidney from lead poisoning ten years ago. Ill with headaches for two years. The case was watched for the last year, when the blood pressure was 230 to 200 mm., and it slowly terminated in a pure uræmic death with wasting, coma, and a little vomiting in the last seven days. Athero-sclerosis well marked in aorta. Heart 17 oz.

Glands 8 hrs. post-mortem, 4.5 and 4.2 gm. respectively.

No cortical adenomata. Lipoid extremely abundant. Medulla certainly not enlarged.

Case 54. Man, aged 68. Ill for one year. Blood pressure 170-80 mm. Sudden death in twenty-four hours by thrombosis of basilar artery. Temperature rose from 97° to 102°. Fibrosed, small kidneys. Heart not hypertrophied, and very little atheroma.

Glands 18 hrs. post-mortem, 3.21 and 3.2 gm.

Fat abundant, no cortical adenomata; medulla rather large.

Case 55. Woman, 61. Generalized arterio-sclerosis, the kidneys being moderately diseased. Blood pressure 200; heart 22 oz.; aorta very atheromatous. Kidneys 4 oz. each. Death by cerebral degeneration and coma, rather than by uræmia. Liver shrunken to 31 oz., yet adrenals enlarged.

Glands 7 hrs. post-mortem, 7.22 gm. = 4.3 mg.

6.74 gm. = 4.3 mg.

Fat very full, and many small adenomata.

Case 56. Man, aged 38. Lead poisoning twenty years ago. Two years of chronic uræmia with vomiting. Blood pressure 270 mm. Death with coma and blindness developing progressively in last three weeks. Temperature sub-normal. Small red kidneys, 2 oz. each. Heart 13½ oz. Slight atheroma of aorta.

Glands 12 hrs. post-mortem, lipoid very abundant.

Small cortical adenomata. Medulla unusually small. 5.64 gm. and 5.32 gm.

Case 57. Woman, aged 50. Ill for two years with chronic uræmia, and acute development with fits, drowsiness and scanty urine for last nine days.

Blood pressure 170 mm. Temperature subnormal. Small white kidneys $2\frac{1}{2}$ oz. each. Heart 13 oz. No atheroma. Slight pleurisy and pneumonia.

Glands 6 hrs. post-mortem, lipid abundant and small adenomata; medulla extremely small.

5.56 gm. = 0.4 mg.

6.89 gm. = 0.4 mg.

Case 58. Man, aged 31. Acute nephritis twelve years ago. Good health until uraemic restlessness and pulmonary oedema developed in last four weeks. Lungs very oedematous, with great dyspnoea and distress, though semi-comatose. Blood pressure 200 mm. Heart 18 oz. No atheroma. Small red kidneys.

Glands 12 hrs. post-mortem, 7.1 gm., fat full, small adenomata.

7.5 gm. = 2.1 mg.; the increased weight of the glands was largely due to oedema.

Case 59. Man, aged 42. Polyuria for twenty years. Uraemia with vomiting for six months. Ascites. Blood pressure 180 to 140 mm. Pericarditis and slight fever. Heart 21 oz. Very slight atheroma. Congenital hydronephrosis.

Glands 8 hrs. post-mortem, full of fat; no adenomata.

5.25 gm. = 3.5 mg.

5.55 gm. = 3.2 mg.

Case 60. Man, aged 30. Uraemic vomiting and headaches for ten months; later retinitis and fits. Blood pressure 200 mm. Temperature 98° , despite pericarditis. Red, fibrosed kidneys. Heart 21 oz. Very slight atheroma.

Glands 16 hrs. post-mortem, 6.65 gm., full of fat and small adenomata.

9.63 gm. with very large cortical adenomata = 3.1 mg. adrenalin.

Case 61. Boy, aged 16. Chronic nephritis for five years. Blood pressure 100 mm. Death by chronic uraemia with drowsiness. Fibrosed kidneys $1\frac{1}{2}$ oz. Heart $7\frac{1}{2}$ oz. No atheroma.

Glands 18 hrs. post-mortem, 4.72 and 4.05 gm., full of lipid; no autolysis.

This slight enlargement of the adrenals had not caused any precocious growth of the boy, for he had an infantile appearance of 12 years old, such as is frequently seen in children with chronic kidney disease.

In nine other cases with high blood pressure similar results were found, the glands being sometimes a little enlarged by cortical adenomata, but otherwise normal in their contents. The presence of the adenomata was not directly related to the extent of atheroma in the aorta.

Secondary infections with fever brought with them the usual result, partial loss of the cortical lipid, just as it would in the absence of kidney disease.

Case 62. Woman, aged 37. Uraemic headaches for six months. Blood pressure 190 mm. Death by respiratory obstruction from rapidly spreading impetiginous infection of nose and face. Temperature 100° . Small, white granular kidneys.

Glands 3 hrs. post-mortem, 4.5 gm., fat considerably exhausted.

2.53 gm. with irregular areas of old cortical atrophy. No adenomata. No increase of medulla.

B. Chronic parenchymatous nephritis and large smooth kidneys. There were four cases, and the results were identical with those of interstitial nephritis.

Case 63. Man, aged 33. Albuminuria and dropsy three years, following acute nephritis. Uraemia last six months. Blood pressure 180 mm. Comatose at death. Heart 18 oz. A little yellow atheroma. Large smooth kidneys.

Glands 20 hrs. post-mortem, lipoid fair; medulla full size.

5.1 gm.

3.97 gm.

Case 64. Man, aged 30. Oedema and headaches, following acute nephritis one year ago. Retinitis. Blood pressure 200 mm. Large white kidneys. Heart 14 oz. No atheroma.

Glands 18 hrs. post-mortem, lipoid abundant and small adenomata.

5.46 gm. = 5 mg.

Case 65. Man, aged 41. Bright's disease $7\frac{1}{2}$ years ago. Oedema three months. Blood pressure 150 mm.; pericarditis and slight broncho-pneumonia. Temperature 99°. Slight atheroma. Heart 21 oz. Kidneys fibrosed and small, $3\frac{1}{2}$ oz.

Glands 20 hrs. post-mortem, no adenomata, fat full.

4.88 gm. = 2.45 mg.

3.41 gm. = 1.9 mg.

Summary.

From all this tedious detail emerges at any rate one generalization, that the cortical lipid is stored and consumed under conditions entirely different from those which control the body fat in general. The starvation of cancer, diabetes, and especially of anorexia nervosa strips the fat from the body: it leaves unchanged the lipid of the adrenal cortex. Pathological intoxications, such as that in diphtheria, increase the apparent fat in the heart and kidney: they only exhaust the cortical lipid. Except in the degenerating areas of the foetal cortex there is no abnormal accumulation of fat in the adrenal under ordinary conditions of disease. On the contrary, there is actual loss. The lipid vanishes with great rapidity in acute septic fevers, slowly in chronic fevers; and it is also diminished in severe haemorrhage and anaemias.

The load of lipid is not directly related to that of adrenalin. It is true that both are reduced in septic fevers, but there are several conditions in which the adrenalin is lessened without any change in the lipid. The cleanest example of this was in Cases 7 and 8, where circulatory failure and mental distress had exhausted the medulla, yet the cortical fat seemed normal. So, too, the adrenalin is lessened by the strain of a surgical operation, which leaves the lipid unaffected. In my experiments on cats, exhaustion of the adrenalin was produced in various ways; in none of these was any alteration detected in the cortical fat, and there was no suggestion that the latter was controlled, like the adrenalin in the medullary cells, by the splanchnic nerves.

The nature of this loss of cortical lipid cannot be explained by the evidence at present available.

1. It might be that the mere rise of temperature in the fevers carries it

away by a change of physical state. Such non-septic hyperpyrexia as occurs in some fatal cerebral haemorrhages would be of great value in answering this question as to whether the loss is caused by poisoning or simply by the rise of temperature. I have not had the opportunity for such an analysis apart from the exhausting complications introduced by broncho-pneumonia. But Case 45, where a final temperature of 107° was reached after a cranial operation, comes near to the desired condition, and in it the fat was normal. Experimentally I have compared the glands in cats under ether, of which the one was cooled to 96° , rectal temperature, and the other heated to 107° (normal 100° to 102°) for three hours. No alteration could be detected in the adrenal lipid. Hence it does not seem probable that this simple physical change suffices to explain the disappearance of the lipid.

2. A second suggestion is that the cortex is concerned in upholding the cholesterin ester content of the blood, and that the latter may play an essential part in resisting the poisonous effect of the bacterial infections, while its excess may lead to atheromatous changes in the walls of the blood-vessels. Workers abroad have shown that the cholesterin percentage in the blood sinks in fevers. Some such relationship would also serve to explain the frequent diminution of the adrenal lipid in severe haemorrhages, when these substances may be lost to the body with the escape of the blood. There is no satisfactory experimental evidence on this point. Gardner and Lander (24), by chemical analyses in starved cats, found that the cholesterol of the adrenals fell during starvation, while that of the blood was still upheld. Weltmann was inclined to think that infections in guinea-pigs caused at first an actual increase in the lipid, and that exhaustion followed rapidly as the intoxication increased.

On the other hand, the especial growth of the cortex in the human foetus—provided that the cerebral hemispheres of the child are developing to their full measure—and its partial atrophy after birth, just when the infant is exposed to a world of new bacterial infections, seem totally opposed to any theory which would connect the lipid with the febrile reactions of septic infection.

3. Bodily growth and sexual maturation are undoubtedly controlled to some extent by the adrenal cortex. The evidence reviewed by Glynn (25) is conclusive on this point. Morphologically the cortical cells are related to the interstitial cells of the generative glands, upon which in the testicle the male characteristics of the body depend. The cells in the testis, like the lutein cells of the ovary, contain a lipid closely resembling that of the adrenal. But it is obvious that this fatty substance is unlikely to be the material by which sexual maturation is effected, if it can disappear in the course of a couple of days' fever. And it must be remembered that the lipid is not present in the adrenals of all mammals, nor always in the testicles. The growth function is probably to be ascribed to some other secretion of the cells than the lipid. Curiously, the fat in the sex glands was found to show changes closely parallel to that of the adrenal cortex. Thus it was abundant in the lutein cells of the emaciated woman (Case 4); it was lost in the febrile disease of Case 29, and moderately

exhausted in Case 79. Similar changes were seen in the testicles, though the comparison was not analysed with sufficient detail.

I have not seen any examples of sexual precocity associated with cortical tumours, and no pathologist, into whose hands such material has fallen, has, so far as I am aware, considered the presence or absence of lipid in the growth. Hypernephromata arising in the kidney in some instances do secrete a lipid. In two cases examined by me, the lipid was also secreted by the cells in the secondary deposits elsewhere, yet the patients exhibited no special symptoms that could be ascribed to this material, and no atheromatous changes were found in their aortae.

Adenomata are common in the cortex, and they are always abundantly laden with lipid. Their cells, though well vascularized, do not part with their fat so quickly as does the normal cortex in fever, a fact which suggests that there may be some obscure nervous control of the cortical cells. They arise chiefly from the cortical islets embedded in the medulla, but they do not cause pressure symptoms, as do those of the thyroid or pituitary; and it cannot be said that their presence is a mark of special disease and an index that the gland's functions have of late been either exalted or depressed. In five of the cases quoted in this paper the adenomata were very large, so much so as to double the weight of the gland. Two were tuberculous patients, but this seemed to be only a chance association. One was from chronic renal disease.

Small, multiple adenomata of the cortex are very frequent, and they do tend to appear with greater frequency in renal cases, though Cases 53, 54, 59, and 62 show that the phenomena of kidney disease and high blood pressure could be developed for a long time without the growth of these nodules. The relationship of the cortical lipid to renal disease and to atheroma is discussed later.

ADRENALIN.

The results of the analyses for adrenalin may be briefly recapitulated. As stated earlier, the normal gland of a healthy man weighs between 4 and 5 gm. and yields from 4 to 5 mg. of adrenalin by my method of assay.

Children. I have not been able to collect material enough to show to what extent the adrenalin load alters at different ages of life. Schmorl and Ingier stated it to be practically uniform for ages from 10 to 40, with a slight falling off in old age. They found the average load for one gland at birth to be 0.08 mg., at 2 years 0.6 mg., at 5 years 1.5 mg., at 10 and onwards 2.0 mg. Their figures probably record not more than half the real load, though they may be enough for comparison relatively to one another. Goldzieher gives the figures 0.5 mg. for the gland of a new-born child, 2 mg. for an adult; and he does not attempt to trace the increase of the load in early youth.

My own observations gave slightly different results. At birth the medulla of the adrenals is small, but there is a large mass of chromaffine cells outside

the gland in the organ of Zuckerkandl, to which Kohn has given the better name of the paraganglion aorticum. Biedl and Wiesel (6) proved that this paraganglion contains adrenalin. I measured the total amount that could be extracted and found it to be very considerable, nearly 1 in 500 of the entire weight of the paraganglion. On the other hand, from the adrenal gland itself at birth only a trace of adrenalin could be obtained.

Case 66. Full-term child : transverse presentation. Death in delivery.

Gland 3 hrs. post-mortem, 3.21 grm. = 0.012 mg.

Entire paraganglion aorticum of both sides 0.1 grm. = 0.12 mg.

Case 67. Full-term child : breech presentation and death in delivery.

Gland 4 hrs. post-mortem, 2.7 grm. = 0.009 mg.

Entire paraganglion 0.11 grm. = 0.24 mg.

Case 68. Full-term child six days old. Normal delivery, but death from asphyxia in succession of fits. No cause of death found. The adrenals showed uniform enlargement of the cortex with no special features.

Gland 14 hrs. post-mortem, 5.72 grm. = 0 mg. adrenalin.

Kidney 15.52 grm.

Entire paraganglion 0.125 grm. = 0.225 mg.

Kidney and adrenal of other side 27.7 grm.

The weight of a normal adrenal at birth is slightly above 2 grm., and this figure is liable to be abnormally increased by congestion of the gland with blood when the death is asphyxial, as in Case 66. Consequently Case 68 was at least double the normal size. No special features, except the unexplained fits, could be found in connexion with this hypertrophy.

These observations show that the adrenal just before birth is in no respects comparable with the gland of post-natal life. The foetal cortex degenerates after birth, and is supplanted by a fresh growth (19). The foetal medulla before birth contains practically no adrenalin, for the latter is provided by the chromaffine tissues outside the gland in the close neighbourhood of the sympathetic ganglia; and these chromaffine masses, like the foetal cortex, degenerate soon after the child is born, when the medulla begins to assume its proper function.

I have no figures for the glands of children in health. Those in disease may be quoted here, but it should be remembered that they are all under conditions leading to partial exhaustion.

Case 16. 2 years and 8 months. Diarrhoea 1 week.

Gland 12 hrs. post-mortem, 1.62 grm. = 0.31 mg.

Case 14. 2 years and 8 months. Post-diphtheritic paralysis of diaphragm; asphyxia and broncho-pneumonia.

Gland 4 hrs. post-mortem, 1.56 grm. = 0.7 mg.

Case 15. 3½ years. Haemorrhagic diphtheria 2 days.

Gland 17 hrs. post-mortem, 1.4 grm. = 0.37 mg.

Case 69. Child 5½ years. Toxic diphtheria.

Gland 32 hrs. post-mortem, 2.2 grm. = 0.55 mg.

Case 46. Girl, 13 years. Death after 2 hours' operation under chloroform.

Glands 18 hrs. post-mortem, 2.65 grm. = 1.8 mg.
2.46 grm.

Case 19. Boy, 13 years. Chronic septic meningitis for 5 weeks.

Glands 5 hrs. post-mortem, 4.75 grm. = 2.0 mg.
4.52 grm.

These figures give no reliable indication of the rate at which the glands grow, nor of the age when they attain their adult load of adrenalin.

Exhausting Conditions.

Fright, anaesthetics, cerebral injury with reactive rise of blood pressure, excitation of afferent nerves, and bacterial intoxications have been proved by my experiments on cats to exhaust the residual adrenalin through the splanchnic nervous control of the glands.

The following examples will illustrate the extent of this loss and the rapidity with which it occurs. In each experiment the splanchnic nerve to the gland was cut on one side. By this section one gland was isolated from the exhausting influences, and so kept in a resting state to serve as a measure of the original load of adrenalin at the time when the experiment was begun.

Ether 6 hours: resting gland 0.26 mg.; exhausted 0.07 mg.

Chloroform $5\frac{1}{2}$ hrs.: resting 0.21 mg.; exhausted 0.08 mg.

Cerebral haemorrhage and destruction of brain 6 hrs.: resting 0.19 mg.; exhausted 0.03 mg.

Morphia 6 hrs., the drug being merely excitant to cats: resting 0.22 mg.; exhausted 0.07 mg.

It was also proved that cats which had been recently admitted to the laboratory and were alarmed and suspicious of their new surroundings always had much less adrenalin in their glands than those which had been in a longer time and become happy and contented. These factors, which lead to quick loss of adrenalin in a cat, must certainly act in man also. They need consequently to be considered in each separate case with especial reference to the conditions that immediately preceded death, before any conclusions can be drawn with regard to the general exhausting influences of the disease that led to death. Moreover, the analyses quoted in the earlier pages of this paper show that after death there is a steady loss of adrenalin by autolytic changes, which increases hour by hour and in twenty hours may amount to 15 or 20 per cent. of the total. This also must be taken into consideration, so that it becomes necessary to name for each case the time that elapsed post-mortem before the glands were extracted for analysis. With all these complex conditions affecting human pathological material, one is therefore compelled to adopt the tedious method of quoting each separate case in detail, so that each may be judged individually with regard to these details. It is quite misleading to calculate averages from the figures

given; nor can the examples quoted be tabulated in columns for a comparison except of the roughest nature.

Effect of Anaesthesia.

Case 46. Girl, aged 13. Normal health. Chloroform for 2 hours.

Gland 18 hrs. post-mortem, 2.65 grm. = 1.8 mg.

Case 51. Man, aged 42. Acromegaly, chloroform for 3 hours.

Gland 15 hrs. post-mortem, 7.83 grm. = 4.2 mg.

Case 45. Woman, aged 36. Cerebellar decompression under open ether. Death 15 hours later.

Gland 12 hrs. post-mortem, 3.63 grm. = 1.5 mg.

Case 43. Man, aged 57. Death $1\frac{1}{2}$ hours after extensive operation for removal of glands from the neck, which lasted 3 hours under intravenous ether.

Gland 5 hrs. post-mortem, 3.59 grm. = 3.6 mg.

3.7 grm. = 3.6 mg.

Case 44. Woman, aged 47. Death 8 hours after operation for removal of vagina, which lasted 45 minutes under intravenous ether.

Gland 8 hrs. post-mortem, 4.76 grm. = 3.2 mg.

These examples suggest a loss of adrenalin under anaesthetics, varying from 20 to 50 per cent. and insufficient to cause death. The differences in the figures in each case illustrate the difficulty of deduction from human material, and in themselves would hardly have been enough to justify the belief that anaesthetics do exhaust the medulla. In the cat the result was quite clear, because the gland of one side taken out at the commencement of anaesthesia could be contrasted with the other, which was removed at the end of the experiment. Under these experimental conditions the adrenalin load was reduced by 50 per cent. when ether or chloroform had been administered for four or five hours.

Cerebral Compression.

Here it is necessary to distinguish two types. First come those cases, as in a cerebral haemorrhage, where the rise of pressure is sudden and the vasomotor centres in the medulla react energetically to produce the characteristic slow pulse, and the rise of blood pressure with presumably a simultaneous call upon the adrenals. These conditions were proved to exhaust the adrenalin in cats. But in the second group, as especially with tumours and spreading oedema of the brain, there is more often a progressive coma that deepens into a quiet sleep and so reaches the end without any emphatic features of bulbar excitation. In these the adrenals show little loss.

Case 70. Man, aged 49. Sudden and extensive pontine haemorrhage; death in eleven hours. For the first six hours the blood pressure was 250 and

temperature 100°; then it sank to 130, and so progressively to death. Heart 16½ oz.; kidneys slightly fibrosed.

Glands 12 hrs. post-mortem, 4.4 grm. = 1.2 mg.
4.3 grm. = 1.36 mg. fat normal; no adenomata, and medulla certainly not enlarged.

Case 71. Woman, aged 49. Extensive haemorrhage in right external capsule which slowly forced its way inwards to the ventricles. She rapidly became unconscious and died in ten hours. Blood pressure 230-40, and axillary temperature 104.6°. Kidneys slightly fibrosed; heart 10 oz., and slight atheroma of aorta.

Glands: Left 5 hrs. post-mortem, 4.22 grm. = 1.12 mg.
Right 10 hrs. post-mortem, 4.38 grm. = 1.0 mg. No autolysis, fat full, medulla small.

These were undoubted examples of exhaustion in the attempt made by the vaso-constrictor centre to sustain the pressure and the cerebral circulation.

Case 72. Man, aged 56. Post-parietal glioma, with headache and vomiting for one month before death; fair recovery; and then rapidly deepening coma in last thirty hours with slight left hemiplegia. Final blood pressure not measured.

Glands: Left 2 hrs. post-mortem, 2.82 grm. = 0.9 mg., being irregularly atrophied.
Right 22 hrs. post-mortem, 6.65 grm. = 1.25 mg., fat full, and no autolysis.

Case 25. Man, aged 55. Pachymeningitis haemorrhagica; two days' coma. Blood pressure 160 and terminal fall.

Glands 6 hrs. post-mortem, 4.95 grm. = 3.0 mg.
4.85 grm.

Case 73. Man, aged 61. Large cystic frontal glioma. Ill for four months with apraxia and recurrent cerebral coma. No vomiting. Blood pressure 140-60. Became very emaciated towards end.

Glands 2 hrs. post-mortem, 4.27 grm. = 4.0 mg.
4 hrs. post-mortem, 5.68 grm. = 4.0 mg.

Case 74. Woman, aged 32. Glioma of temporo-sphenoidal lobe, causing death by cerebral compression. Slow development of quiet coma resembling sleep. Blood pressure normal at 120. Recovered full consciousness after parietal decompression, but died suddenly thirty-six hours after.

Glands 7 hrs. post-mortem, 5.45 grm. = 2.4 mg.
5.9 grm. = 2.5 mg.

Here the anaesthetic and the operation complicated the result and were in themselves partly responsible for the moderate loss of adrenalin. There was no rise of blood pressure to exhaust the glands.

Heart Failure.

Case 75. Man, aged 46. Old mitral regurgitation with much oedema and ascites for nine weeks. Auricular fibrillation. Sudden death when commencing to improve under digitalis. Heart much enlarged.

Gland 15 hrs. post-mortem, 3.35 grm. = 3.6 mg.

Case 76. Woman, aged 21. Old aortic regurgitation and anginal attacks for years. No oedema; well nourished. Sudden death after two or three weeks of recurrent pain and moderate distress. Heart 27 oz.

Glands: Left 2 hrs. post-mortem, 3.1 grm. = 3.2 mg.

Right 20 hrs. post-mortem, 4.45 grm. = 3.25 mg., enlargement of this gland being chiefly by cortical adenomata.

Assay of old extract of left gland, after standing 18 hrs. = 3.0 mg.

This may be accepted as the actual true load in the course of chronic heart disease, insomuch as death occurred suddenly. But in the next two instances of acute heart failure, the sufferer was in obvious mental distress for the two or three days preceding death, and though the blood pressure was low and the pulse was feeble, the vasomotor nerves were doubtless strained to their uttermost to help the dying heart. Observations on the effect of fright in exhausting the adrenalin in cats emphasize the need to realize how rapidly the glands may be emptied in man during emotional anxiety and distress.

Case 7. Girl, aged 16. Chronic valvular disease. Acute collapse with great mental distress in last thirty hours.

Glands 9 hrs. post-mortem, 4.35 grm. = 0.7 mg.

4.75 grm. = 0.7 mg.

Case 8. Woman, aged 26. Three years' illness from hypertrophied feeble heart. Complete cardiac failure in last few days with much distress.

Gland 8 hrs. post-mortem, 4.7 grm. = 0.2 mg.

On the other hand the next case showed little loss of adrenalin, despite the cold skin and feeble circulation, presumably because the patient was apathetic and reactionless.

Case 9. Man, aged 35. Mitral stenosis and auricular fibrillation. Death by slowly progressive thrombosis within auricles. No mental distress.

Glands 2 hrs. post-mortem, 5.42 grm. = 2.3 mg.

5.78 grm. = 2.3 mg.

Malignant Endocarditis.

Heart failure is added to septicaemia, but the latter by its intoxication is the chief cause of death. The adrenalin is exhausted, but not so much as is the lipoid; whereas in the preceding cases the lipoid was not affected at all.

Case 23. Gland 18 hrs. post-mortem, 5.39 grm. = 0.75 mg.

Case 22. Glands 20 " " 6.3 grm. = 0.75 mg.

4.7 grm. = 0.35 mg.

Case 20. Gland 13 " " 6.47 grm. = 2.1 mg.

Case 21. " 8 " " 3.72 grm. = 2.3 mg.

Case 77. Woman, aged 48. Old rheumatic heart. Malignant endocarditis for five weeks, with many streptococci in blood and fever, 101° to 103°.

Gland 24 hrs. post-mortem, 4.5 grm. = 1.5 mg.

Pneumonia.

Case 10. Man, aged 37. Acute pneumonia three days.

Gland 5 hrs. post-mortem, 10.35 grm. = 1.45 mg.

Case 11. Man, aged 42. Pneumonia seven days.

Gland 22 hrs. post-mortem, 7.4 grm. = 1.2 mg.

Case 13. Man, aged 42. Pneumonia six days, and old syphilitic aortic disease.

Glands 4 hrs. post-mortem, 7.23 grm. = 2.5 mg.

6.72 grm. = 2.5 mg.

Other Septic Infections.

Case 18. Man, aged 29. Perinephritic abscess and pyaemia.

Gland 20 hrs. post-mortem, 7.72 grm. = 2.5 mg.

Case 78. Man, aged 26. Gangrenous broncho-pneumonia and empyema for four weeks. Temperature 100° to 103°.

Gland 18 hrs. post-mortem, 5.6 grm. = 1.75 mg.

Case 79. Woman, aged 18. Small chronic empyema for five years, but otherwise in good health. Estlander operation was followed by death seventeen days later with abscesses in chest wall, in occipital lobe of brain, and with pus in ventricles. Fever 101° to 104°.

Glands 18 hrs. post-mortem, 7.98 grm. = 1.4 mg.

5.63 grm. = 1.25 mg. moderate fat in cortex,
and also in corpora lutea.

Case 80. Man, aged 48. Closed abscess in lung with rigors and high fever in last week. Haemorrhage from old gastric ulcer. In final twenty-four hours temperature rose from 105° to death at 106°.

Glands 9 hrs. post-mortem, 4.59 grm. = 2.6 mg.

5.68 grm. = 2.5 mg.

In all these septic states the weight of the gland tended to be increased and the lipoid diminished; and in all there was some exhaustion of the adrenalin, though not so great as in the case of cardiac failure, and probably not so great as in itself to endanger life.

Tuberculosis.

Case 35. Man, aged 29. Addison's disease; no fever.

Gland 8 hrs. post-mortem, 10.1 grm. = 0.03 mg.

Case 36. Man, aged 34. Chronic Addison's disease for ten years. Atrophied tuberculous glands.

Gland 6 hrs. post-mortem, = 0 mg.

Case 33. Man, aged 28. Miliary tuberculosis.

Gland 24 hrs. post-mortem, 7.8 grm. = 1.4 mg.

Case 32. Woman, aged 45. Pulmonary and intestinal tuberculosis.

Gland 8 hrs. post-mortem, 8.8 grm. = 2.14 mg.

Case 81. Woman, aged 35. Chronic tuberculous salpingitis and enteritis with miliary tuberculosis of lungs and peritoneum. Temperature 101° and 103°.

Glands 7 hrs. post-mortem, 5.23 grm. = 1.2 mg.

6.08 grm. = 1.2 mg., large tuberculous areas.

Anaemia.

Case 41. Woman, aged 33. Death caused in nineteen days by haemorrhage from gastric ulcer, and this was associated with mild malignant endocarditis.

Gland 7 hrs. post-mortem, 6.7 grm. = 3.25 mg.

Case 42. Man, aged 30. Splenic anaemia with repeated haemorrhages.

Gland 8 hrs. post-mortem, 4.26 grm. = 2.5 mg.

Case 82. Woman, aged 34. Multipara. Severe ante-partum haemorrhage in eighth month. Bleeding for four hours; cervix dilated and child delivered under chloroform; patient died two hours later from shock and tear of vagina.

Glands: Right 4 hrs. post-mortem, 4.5 grm. = 1.47 mg.

Left 21 hrs. post-mortem, 5.92 grm. = 2.8 mg., fat very abundant.

Case 83. Woman, aged 24. Chronic ulcerative colitis. Haemorrhage in last few days but not of a serious nature; sudden death by pulmonary embolism. No fever.

Glands 7 hrs. post-mortem, 4.14 grm. = 2.0 mg.

4.55 grm. = 2.1 mg., fat full.

Loss of blood seems to affect the adrenalin much less than might have been anticipated from the disturbances brought about at the same time in the vascular adjustments.

Other Conditions.

Case 5. Man, aged 39. Ulcerative colitis and extreme emaciation. No fever; death by diarrhoea and exhaustion.

Gland 10 hrs. post-mortem, 4.8 grm. = 1.8 mg.

Case 4. Woman, aged 29. Anorexia nervosa with great emaciation. Final septic pneumonia for one week.

Glands 14 hrs. post-mortem, 5.82 grm. = 2.0 mg.

5.2 grm. = 2.0 mg.

Case 50. Man, aged 62. Diabetic coma.

Gland 8 hrs. post-mortem, 6.8 grm. = 2.0 mg.

Case 84. Man, aged 36. Tetanus with moderate locking of jaw, and marked contraction of trunk muscles for four days. Sweating with muscular strain, but no fever and no mental alarm. Died in sudden spasm during administration of chloroform. Both psoas muscles found to be ruptured.

Glands 12 hrs. post-mortem, 3.87 = 2.31 mg., fat normal.

3.88 = 2.31 mg.

Case 26. Woman, aged 42. Cancer of lung and thoracic effusions. Ill four months. Sudden death by pulmonary embolism.

Gland 18 hrs. post-mortem, 6.32 grm. = 4.2 mg.

Here again the figures are not very conclusive. The last case (26) shows that the invalid life entailed by cancer and some mechanical embarrassment of the heart and lungs does not of necessity reduce the adrenalin. But as a rule there is considerable exhaustion in all the septic illnesses, and especially so in acute miliary tuberculosis. Nothing can be said more definitely than this. Once more appears the contrast between the cortical lipoid and the adrenalin. The fat was abundant in Case 5, where the adrenalin was low; there was hardly any in Case 41, where the adrenalin was, for illness, high.

Mott and Halliburton thought that the adrenalin was especially reduced in chronic disease, such as tuberculosis, cancer, or chronic Bright's disease, whereas a good reaction was found by them in pneumonia. This can hardly be regarded as other than a mistake. It is acute febrile illness which especially exhausts both the cortex and the medulla of the gland: the chronic ailments depreciate the stores to a much less serious degree.

For convenience I have tabulated some of my analyses in a series of what seemed to me typical cases. Each is an individual analysis, for, as was urged earlier, the conditions before and after death varied so widely in the several examples of each particular disease that the calculation of an average figure would not represent the change with any greater accuracy. So many slight factors affect the load of adrenalin found by assay that it is unwise to notice any difference of less than 0.5 mg., and figures in the second place of decimals are not worth recording.

TABLE I.

Cause of Death.		Weight of Gland.	Adrenalin.	Lipoid.
		gram.	mg.	
<i>Child.</i>				
Full term	Asphyxial	2.5	0.01	slight
	Paraganglion	0.11	0.22	nil
2 $\frac{3}{4}$ yrs.	Post-diphtheritic asphyxia	1.6	+ 0.7	
3 $\frac{1}{2}$ yrs.	Haemorrhagic diphtheria	1.4	+ 0.4	moderate
13 yrs.	Chloroform and shock	2.5	1.8	"
<i>Adult.</i>				
	Normal. Accident	4	4.5	full
	Surgical shock	3.7	3.6	"
	Long anaesthesia	—	2 to 3.0	"
	Cerebral tumour and coma	4.2	4.0	"
	Cerebral haemorrhage with raised blood pressure	4.4	1.3	"
	Cancer: sudden death	6.3	4.2	"
	Heart disease:			
	sudden death	3.4	3.6	"
	slow failure and apathetic death	5.5	2.3	"
	acute failure and mental distress	4.5	0.2 to 0.7	"
	with septicaemia of malignant endocarditis	4 to 6	0.7 to 2.0	lost or slight
	Haemorrhage from:			
	splenic anaemia	4.2	2.5	full
	gastric ulcer	x	x	slight
	Pneumonia:			
	acute	10.35	1.45	lost
	slow	7.0	2.5	slight
	Pyæmia	7.7	2.5	lost

TABLE I (continued).

Cause of Death.	Weight of Gland.	Adrenalin.	Lipoid.
	grm.	mg.	
<i>Adult (continued)</i>			
Tuberculosis:			
Addison's	10.1	0.3	traces
miliary	7.8	1.4	moderate
acute pulmonary	8.8	2.14	slight
Nephritis:			
parenchymatous	4.8	2.4	full
chronic interstitial:			
uraemia	4.4	—	"
with pericarditis	5.3	3.5	"
arterio-sclerotic	7.0	4.3	"
Acromegaly	7.83	4.2	moderate

Schmorl and Ingier's tabulated results differ from mine, partly because their standard of health, 2.33 mg., was so much lower than what I found, namely 4 mg. Measuring from this standard they record:

A slight increase for pneumonia	2.44 mg.
Slight decrease for septicaemia and malignant endocarditis	2.28 "
Greater decrease for miliary tuberculosis	2.03 "
Increase in acute nephritis	3.01 "
Increase in interstitial nephritis with large heart	3.25 "
Increase in valvular heart disease	3.27 "

The authors dealt with their results with caution, pointing out the difficulties of drawing any deductions from these figures.

Goldzieher's conclusions agree more closely with mine. His standard for one gland of a healthy adult was 2 mg. In septic conditions this fell to 0.75, while the gland became swollen and the cortical lipid was observed to disappear. For chronic nephritis and arterio-sclerosis he found the contents to be 2.9 mg., a slight increase under conditions of high blood pressure which agrees with Schmorl and Ingier but is at variance with the observations that I describe subsequently.

High Blood Pressure and Athero-sclerosis.

In discussing these diseased states there are two separate and distinct theories to be considered, both of which have been developed chiefly by French thought. Shortly after the discovery of the intense vaso-constriction caused by extracts of the medulla, it was naturally suggested that persistently high blood pressure might be explained by hypertrophy of the medulla and too abundant secretion of adrenalin. Adrenalin was later proved to cause atheroma in the aorta when injected repeatedly into the blood-stream; and this observation at once made it possible to ascribe both the high pressure and the atheroma to one and the same cause, excess of adrenalin in the blood from a supposed hypertrophy of the medulla. The theory was of course followed by the statement that the medulla is hypertrophied in such conditions.

The second view is of later origin, and it looks for evidence of disease only in the cortex of the gland, neglecting the problem of the rise of blood pressure. Damage of the kidney makes it impermeable to certain substances which are consequently retained in the body. The lipoids of the cholesterin ester group

may under these conditions appear in excess in the blood and be later deposited in various places in the body,¹¹ much as urates are in the uricaemia of gout. Atheromatous changes in the aorta, and excess of lipoid in the adrenal together with cortical adenomata, would both be visible signs of such a state; and atheroma would then be especially associated with excess of cortical lipoid. Chauffard (13) has demonstrated an increase of cholesterin in the serum of patients with nephritis and arterio-sclerosis (0.27 per cent. to 0.42 per cent.) and correlated this with a high cholesterin percentage in the adrenals. On the other hand, the proved loss of the cortical lipoid in acute septic infections would, in the same way, be harmonized with the observations of Chauffard that the percentage of cholesterin in the blood (0.15 to 0.18 per cent.) sinks in the acute septic fevers, and particularly so in acute pneumonia.¹²

The facts are equivocal with regard to the second view, and they almost exclude the first.

Three measurements are needed to justify the statement that the medulla is overactive in a particular case:

It is necessary to know: (1) The percentage of adrenalin circulating in the blood; (2) the amount of adrenalin that can be extracted from the gland after death; (3) the actual bulk of the medullary tissue.

The argument would be good, if an increase could be demonstrated in all of these three factors. So far as I am aware, it has as yet been proved in none. Stewart's (41) criticisms show that at present no reliable method has been found which proves the presence of adrenalin in the general current of the blood. The substance is easily recognized in the blood of the adrenal vein, but it disappears rapidly from the blood during circulation through other tissues, and consequently it cannot be demonstrated with certainty in the superficial veins of the body, which alone are accessible to clinical study. Borberg (8, p. 399) failed to find any action on the frog's pupil with the blood from cases of nephritis or exophthalmic goitre. Fränkel (23), using the rabbit's uterus as a test organ, also found no increase of adrenalin in the centrifugalized serum of chronic nephritis, whereas in exophthalmic goitre he recorded an increase of from four- to eightfold. In the blood of health he found the total amount of adrenalin to be 12.5 mg., but 50 to 100 mg. in the goitrous disease. These figures are very difficult to accept, considering that the entire store of adrenalin in the two glands in health is only about 10 mg. It is therefore clear that statements with regard to the measurement of (1) are at present to be received with criticism and reserve. The theory does not decide whether the cholesterin bodies are first formed in the adrenal cortex or absorbed by these cells from the excess in the blood-stream. (2) can be determined with fair accuracy. The figures given in this

¹¹ Experiments have been made in St. Petersburg (1 and 14) and in Munich (46) which illustrate the deposition of cholesterin in various tissues of the body, when rabbits were fed with this substance for a long time.

¹² Picard (38) has moreover shown in dogs that the cholesterin of the blood and of the adrenal cortex alike may be lessened by prolonged exercise.

paper show that the residual adrenalin in cases of persistently high blood pressure is of practically the same amount as that seen in death from other diseases. (3) offers a laborious task. The medulla is aggregated chiefly at the venous pole of the gland, in a thick mass from which the laminar extension between the cortex of the triradiate tail is very thin and irregular. A series of sections transversely to the venous axis from pole to pole of the gland are therefore needed for a fair estimate of the bulk of the medulla. Longitudinal sections are very misleading. Accurate measurements of the total bulk of the tissue could be obtained by adding up the areas of all the sections, as was done by Tuckett and myself in the glands of some of the smaller animals (20, p. 339). It seemed an extravagance of labour to attempt this in the human gland, and I was content with the rough naked-eye estimate made by looking at a series of slices.

Obviously it cannot be admitted that the medulla must be enlarged because the gland's weight is increased. Oedema in the last few days of life may double its weight, as conspicuously in the cases of acute pneumonia already quoted. Moreover, the cortex forms probably 80 to 90 per cent. of the entire bulk of the gland,¹³ and it is very prone to increase of mass by irregular adenomata, and even perhaps to alteration of its weight by the variations that occur in the load of lipid. A relatively small change in the cortex would add 1 grm. to the total weight of the gland, whereas an increase of 1 grm. in the medulla would mean that the latter was almost trebled in bulk with the possibility of a similar trebling of its adrenalin load.

This difficulty has been neglected by several writers, who have sought for evidence that high blood pressure in renal disease must be associated with hypertrophy of the adrenal medulla, and being perhaps too eager to believe in the theory were reluctant to criticize the facts. The original observations on this question in France were made by Pilliat (1903) and Vaquez, but most of the French workers since then have abandoned the view. In Vienna it is still upheld by Neusser and Wiesel (1910) upon evidence that is in nowise convincing. Wiesel (49) stated that in chronic renal cases with cardiac hypertrophy the medulla is seen in section to be enlarged. But he does not describe the plane of the section with reference to the varying distribution of the medulla, nor does he give the total weight of the glands, nor measure the amount of residual adrenalin. Further, he admits that such hypertrophy is not always seen in chronic nephritis, and that it is not invariably related to high blood pressure, for he saw it in cases of nephritis where the blood pressure was not raised (35, p. 86).

Philpot (37) weighed the glands of twenty-seven cases, of which nineteen were examples of chronic interstitial nephritis. The average weight of each gland in the high pressure series was roughly 6.0 grm., and rather less than 4 grm.

¹³ I am not aware of any actual measurements of this ratio in the human adrenal. Tuckett and I found that the cortex formed 98 per cent. of the gland in the guinea-pig, 95 per cent. in the rat, 90 per cent. in the rabbit and cat, 85 per cent. in the dog, and only 45 per cent. in the fowl. If similar proportions hold for man, an average healthy gland weighing 4.5 grm. will contain only 0.5 grm. medulla, the latter yielding 4 to 5 mg. adrenalin, or about 1 per cent. of its own weight.

in the others: on section he averred that it was the medulla which showed the hypertrophy and not the cortex. The distinction was not proved. In some of his cases circulatory oedema or septic conditions may have been responsible for a temporary increase of weight of the entire gland; and indeed his evidence is of very equivocal value.

Borberg (9) could find no clear evidence for such hypertrophy of the medulla in man; and Bittorf (7), in definite contradiction of Wiesel, stated that the adrenals may be notably small in kidney disease with high blood pressure. It is true that Schmorl and Ingier, who were prevented by their method of analysis from weighing the glands, found an increase of the residual adrenalin in cases of acute or chronic kidney disease and also of valvular heart disease; but the increase was in their opinion too uncertain to be regarded as proof of a special connexion with athero-sclerosis or high blood pressure. Goldzieher also recorded a slight increase under like conditions.

Owing to the number of causes that may affect the weight or the adrenalin content of the glands, it is desirable to approach the question from the other side; not to seek for examples in which the gland is enlarged and there is also a high blood pressure, but to examine the cases in which with high blood pressure and chronic renal disease the patient dies, slowly or quickly, from simple uraemic intoxication, without any phenomena of secondary infections or circulatory failure. This is the pure form of the disease. If in them the adrenals consistently show no hypertrophy, and no accumulation of adrenalin, then it is reasonable to conclude that medullary hypertrophy does not play the main part in the malady, and that such enlargement as may at times occur in complicated cases is accidental or due to such complications.

I have already given in this paper examples of high blood pressure and renal disease of this clean type. The glands were not enlarged. For comparison, the list is summarized here in tabular form. (See p. 86.) Case 53 was a very good instance, the disease having existed for two years, and being closely watched for the last year (blood pressure 230 to 200); yet the glands were in all respects normal. Whenever the gland was heavier than usual, the increase could be attributed to adenomata of the cortex or to oedema; and in most cases the medulla looked, if anything, rather small on section. In Case 57 it was exceptionally small in bulk and gave a surprisingly low yield of adrenalin. Case 64 was the only one in which the gland was enlarged together with increase of adrenalin; and in it unfortunately the second gland was damaged in removal, so that it could not be ascertained whether the second gland was abnormally small, like that in Case 72, a condition which would lead to compensatory hypertrophy in the gland analysed.

Case 62 suggests a line of argument which might weaken the deduction from these recorded facts. In it one gland was certainly atrophic. It might be urged that in all these high pressure cases the adrenals pass through a phase of abnormal activity, which is then succeeded by failure of power and shrinkage, changes that in themselves might help to determine the fatal issue of the disease.

TABLE II.

Case No.	Age.	Ill.	Blood Pressure.	Death.	Adrenals.	Cortex.	Medulla.	Kidneys.	Weight of Heart.	Aortic Atheroma.
53	51	2 years	200 230	uraemic coma, 7 days	gram. 4.5 4.2	no adenomata	not +	fibrosed 4 oz. each	17 oz.	well marked
54	68	1 year	—	sudden thrombosis basilar aneurism	3.21 3.2	no adenomata	large	fibrosed $5\frac{1}{2}$ and 5 oz.	12	none
62	37	6 months	180 190	respiratory obstruction by cellulitis	4.5 2.53	no adenomata	not +	fibrosed 3 oz. each	11	very slight
65	41	3 months dropsy, nephritis 7 years ago	150	pericarditis	4.88 = 2.45 3.41 = 1.9	no adenomata	—	fibrosed $3\frac{1}{2}$ oz.	21	slight
56	38	2 years	270	uraemic coma, 3 weeks	5.64 5.32	small adenomata	very small	fibrosed 2 oz.	13 $\frac{1}{2}$	slight
59	42	6 months	140 180	pericarditis	5.25 = 3.5 5.55 = 3.2	no adenomata	—	congenital hy- dropnephrosis	21	very slight
70	49	?	250	pontine haemor- rhage, 11 hours	4.4 = 1.2 4.3 = 1.4	no adenomata	—	slight fibrosis 5 oz.	16 $\frac{1}{2}$	very slight
71	49	?	230	capsular haemor- rhage, 10 hours	4.22 = 1.12 4.38 = 1.08	very small adenomata	very small	slightly fibrosed 4 oz.	10	slight
60	30	10 months	200	uraemic fits	9.63 = 3.1 6.55	very large adenomata	—	fibrosed $3\frac{1}{2}$ oz.	21	very slight
55	61	+ 1 year	200	arterio-sclerosis, mental failure	7.22 = 4.3 6.74 = 4.3	many small adenomata	—	arterio-sclerotic 4 oz.	22	very marked
58	31	Nephritis 12 years ago	200	pulmonary oedema, 4 weeks	7.5 = 2.1 7.1	oedematous small adenomata	—	fibrosed 3 oz.	18	none
57	50	2 years	170	9 days' drowsy uraemia	6.89 = 0.4 5.56 = 0.4	small adenomata	very small	fibrosed $2\frac{1}{2}$ oz.	13	none
64	30	Dropsy 10 months	200	3 weeks' oedema and headaches	5.46 = 5.0 ? other	small adenomata	—	large white fibrosed 7 oz. and 6 oz.	14	none
63	33	Dropsy 3 years	180	3 months' headaches	5.1 3.97	no adenomata	large	large white 8 oz. each	18	very slight
61	16	Slight dropsy 5 years	100	uraemic coma	4.72 4.05	—	—	fibrosed $1\frac{1}{2}$ oz.	7 $\frac{1}{2}$	none

This hypothetical rise and fall would be analogous to the conditions of super- and sub-pituitarism, or to exophthalmic goitre succeeded by myxoedema. But clinically the possibility is almost denied by the fact that such patients do not in the last few weeks show a progressive fall of blood pressure. Moreover, in the case quoted, it was the cortex that was atrophied, not the medulla. In all the glands examined, though the medulla was often small, its cells looked healthy under the microscope.

Cerebral haemorrhage kills patients suddenly at the very height of disease, yet their glands are normal (Case 70, 4.4 grm. = 1.2 and 4.3 = 1.36 mg.; and Case 71, 4.22 = 1.12 and 4.38 = 1.08 mg.; partial exhaustion having been caused by the increased intracranial pressure). Hence the hypothesis, that the small size of the medulla and its apparently normal load of adrenalin are to be explained by terminal atrophy of a once exuberant mass of cells, is one that cannot be admitted. The observations given here show that in many cases of kidney disease with high pressure the glands are simply normal; in others they are enlarged by cortical adenomata. In none was there unequivocal increase of residual adrenalin; and yet the conditions of death, except in Cases 70 and 71, were not such as to exhaust the adrenalin.

The tendency towards cortical hypertrophy and the growth of small adenomata is a definite feature of kidney disease. In pure forms of renal fibrosis following old toxic influences, such as that of lead-poisoning, the adrenals may be of normal size, as in Case 53. But the arterio-sclerotic form of fibrosed kidney is particularly associated with enlargement of the adrenal cortex, witness Case 55. Between these are intermediate types; and the distinction is not a very clear one. Atheromatous changes in the aorta do not bear any constant relation to the blood pressure or to the hypertrophy of the adrenal cortex.

Changes in the adrenal cortex, in its bulk and in its load of lipid, are the most manifest of the alterations wrought by disease, whether acute or chronic, in this gland. The medullary tissue, like the cells of the nervous system, seems to be less capable of overgrowth. It parts with its adrenalin under conditions which can be more or less understood by reference to the results of recent experimental work on animals; but there is no satisfactory proof that any form of disease is associated with an excess of such secretion. Hence the problem that must be solved and that seems to offer most in the reward of knowledge is the riddle of the cortical secretion. In this direction a step seems to have been made recently (45) by the isolation from the adrenal cortex of a vaso-constrictor substance akin to that found in defibrinated blood and differing from adrenalin.

Conclusions.

1. The normal adrenal gland of an adult man weighs between 4 and 5 grm. and contains from 4 to 5 mg. adrenalin.
2. There is no proof that the store of adrenalin in the medulla is increased in any disease.

3. The adrenalin is lessened in many infective diseases, but probably not to such a degree as to endanger the circulation.

4. The greatest loss was observed in examples of afebrile acute cardiac failure associated with mental distress in the struggle to live.

5. The lipid of the cortex is stored and lost under conditions entirely different from those which govern the other fats of the body. It does not disappear in extreme bodily emaciation.

6. The cortical lipid vanishes with great rapidity in all acute febrile infections.

7. There is a tendency for it to appear in excess in chronic renal disease, especially in conjunction with athero-sclerosis.

REFERENCES.

1. Anitschkow, *Ziegler's Beitr. z. path. Anat.*, Jena, 1913, lvi. 379, and 1913, lvii. 201.
2. Arnold, *Virchow's Archiv f. path. Anat. u. Physiol.*, Berlin, 1866, xxxv. 64.
3. Aschoff, *Ziegler's Beitr. z. path. Anat.*, Jena, 1909-10, xlvii. 1.
4. Bernard, *Revue de Méd.*, Paris, 1907, xxvii. 977.
5. Bernard, Bigart, and Labbé, *Compt. rend. de la Soc. de Biol.*, Paris, 1903, lv. 120.
6. Biedl and Wiesel, *Pflüger's Archiv f. d. ges. Physiol.*, Bonn, 1902, xci. 434.
7. Bittorf, *Die Pathologie der Nebennieren*, Jena, 1908.
8. Borberg, *Skand. Archiv f. Physiol.*, Leipzig, 1912, xxvii. 342.
9. Borberg, *ibid.*, 1913, xxviii. 115.
10. Cannon and de la Paz, *Amer. Journ. Physiol.*, 1911, xxviii. 64.
11. Chalataw, *Ziegler's Beitr. z. path. Anat.*, Jena, 1913, lvii. 85.
12. Chauffard, Laroche, and Grigaut, *La Semaine médicale*, Paris, 1911, xxxi. 577.
13. Chauffard, *Compt. rend. de la Soc. de Biol.*, Paris, 1911, lxx. 276 and 855.
14. Chauffard, &c., *ibid.*, 1912, lxxiii. 23.
15. Comessatti, *Archiv f. exp. Path. u. Pharm.*, Leipzig, 1910, lxii. 190.
16. Dreyer, *Amer. Journ. Physiol.*, 1899, ii. 203.
17. Elliott, *Journ. Physiol.*, Camb., 1912, xlv. 376.
18. Elliott, *ibid.*, 1913, xlvi; *Proc. Physiol. Soc.*, 15.
19. Elliott and Armour, *Journ. Path. and Bact.*, Camb., 1911, xv. 481.
20. Elliott and Tuckett, *Journ. Physiol.*, Camb., 1906, xxxiv. 350.
21. Federici, *Lo Sperimentale*, Firenze, 1904, lviii. 419.
22. Folin, Cannon, and Denis, *Journ. Biol. Chem.*, Baltimore, 1913, xiii. 477.
23. Fränkel, *Archiv f. exp. Path. u. Pharm.*, Leipzig, 1909, lx. 395.
24. Gardner and Lander, *Biochemical Journ.*, Liverpool, 1913, vii. 584.
25. Glynn, *Quart. Journ. Med.*, Oxford, 1911-12, v. 157.
26. Goldzieher, *Die Nebennieren*, Wiesbaden, 1911, 21 and 124; and *Wien. klin. Woch.*, 1910, xxiii. 809.
27. Kaiserling and Orgler, *Virchow's Archiv f. path. Anat. u. Physiol.*, Berlin, 1902, clxvii. 296.
28. Klinkert, *Berl. klin. Woch.*, 1913, l. 820.
29. Lapworth, *Journ. Path. and Bact.*, Camb., 1911, xv. 254.
30. Loeschcke, *Münch. med. Woch.*, 1910, lvii. 1. 48.
31. Marchetti, *Virchow's Archiv f. path. Anat. u. Physiol.*, Berlin, 1904, clxxvii. 227.
32. McNee, *Quart. Journ. Med.*, Oxford, 1913-14, 221.
33. Mott and Halliburton, *Archives of Neurol.*, Lond., 1907, iii. 123.

34. Napp, *Virchow's Archiv f. path. Anat. u. Physiol.*, Berlin, 1905, clxxxii. 314.
35. Neusser and Wiesel, *Die Erkrankungen der Nebennieren*, Wien, 1910.
36. Parkinson, *Trans. Path. Soc.*, Lond., 1907, lviii. 187.
37. Philpot, *Quart. Journ. Med.*, Oxford, 1909-10, iii. 34.
38. Picard, *Archiv f. exp. Path. u. Pharm.*, Leipzig, 1913, lxxiv. 450.
39. Reinhardt and Creutzfeldt, *Ziegler's Beitr. z. path. Anat.*, Jena, 1913, lvi. 465.
40. Schmorl and Ingier, *Deutsch. Arch. f. klin. Med.*, 1911, civ. 125.
41. Stewart, *Journ. Exp. Med.*, N. York, 1911, xiv. 377 ; and 1912, xvi. 502 ; also Stewart and Zucker, *ibid.*, 1913, xvii. 152 and 174.
42. Stoerk, *Wien. klin. Woch.*, 1908, xxi. 282.
43. Thomas, *Ziegler's Beitr. z. path. Anat.*, Jena, 1911, l. 283.
44. Tschoboksaroff, *Pflüger's Archiv f. d. ges. Physiol.*, Bonn, 1910-11, cxxxvii. 59.
45. Voegtlin and Macht, *Journ. Amer. Med. Assoc.*, 1913, lxi. 2136.
46. Wacker and Hueck, *Archiv f. exp. Path. u. Pharm.*, Leipzig, 1913, lxxiv. 416.
47. Weltmann, *Ziegler's Beitr. z. path. Anat.*, Jena, 1913, lvi. 278.
48. White, *Proc. Roy. Soc. Med.*, Obstet. Sec., Lond., 1911-12, vii. 247.
49. Wiesel, *Wien. med. Woch.*, 1907, lvii. 674.

DESCRIPTION OF DRAWINGS.

PLATE 5, FIG. 1. *Loaded Gland.* The cortical cell columns are laden with scarlet-stained lipid: doubly refractive crystals are not represented. In this fully loaded state no blue stain is taken by the cell except in the nucleus. The drawing illustrates a chance feature of interest. The adrenal was unusually adherent to the kidney, and a vagrant renal tubule (*r.t.*) lies twisted in the substance of the cortex, which it penetrated nearly as far as the medulla of the gland.

PLATE 5, FIG. 2. *Exhausted Gland.* The outer zone of the cortex is figured in the drawing. The cells are for the most part empty of fat. Blood lies in the capillaries (*c.*) between the cortical columns, and also in distended spaces (*s.*) apparently within the columns. The patient died of asphyxia in septic meningitis: fever had exhausted the cortical fat, and the asphyxia caused haemorrhage and congestion. The small blue cells (*b.*) at the periphery are immature cortical cells.

PLATE 6, FIG. 3. *Loaded Adenoma in exhausted Gland.* To the right are the scarlet-stained cells of the adenoma (*ad.*), arranged in typical masses within a capillary network. The adenoma is enveloped by a thin shell of dark blue medullary cells (*med.*), which were carried outward as the adenoma spread from its origin in a cortical islet in the medulla. To the left of this are the cortical cell columns (*col.*), slightly distorted by pressure, and exhausted of lipid except in the extreme peripheral rim. The exhaustion was caused by fever.

PLATE 6, FIG. 4. *Cortical Cells in Addison's disease.* Some of the cortical cells are large and laden with lipid (*l.*); others are strangled by inflammatory round cells and exhausted (*e.*). The giant cell systems and the hyaline fibrosis of the tuberculous inflammation occupy the areas from which the cortical cells have vanished (Case 34).

PLATE 7, FIG. 5. *Islet of Adrenal Cortical Cells embedded in Kidney.* The cells are loaded with lipid and identical in all respects with those of the normal cortex. They grow freely intermingled with those of the renal tubules and without a capsule of demarcation. Cells of a similar character may be recognized in Grawitz's variety of malignant renal tumours. In this case the adrenal gland was closely attached to the kidney and offshoots from its cortex could be traced directly into the heart of the kidney.

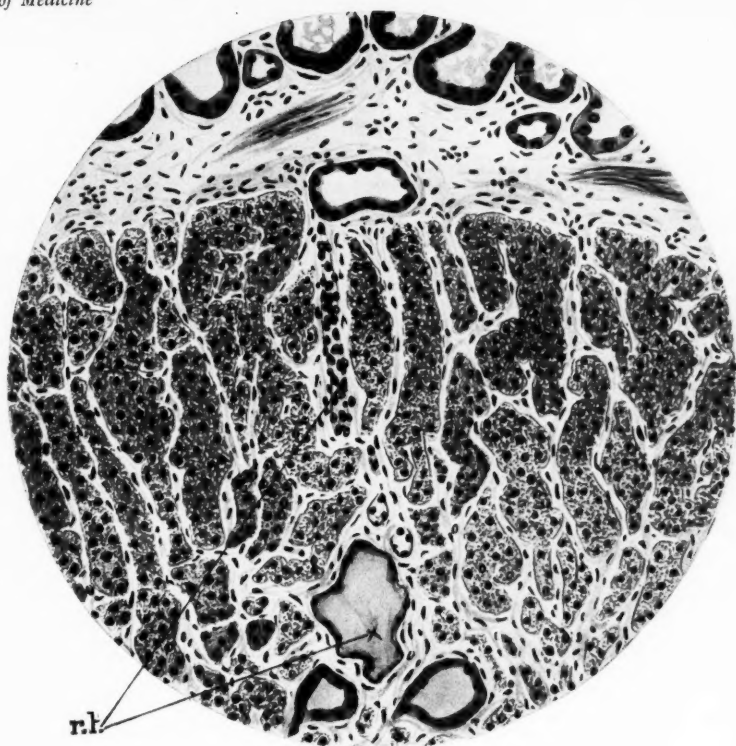


Fig. 1.

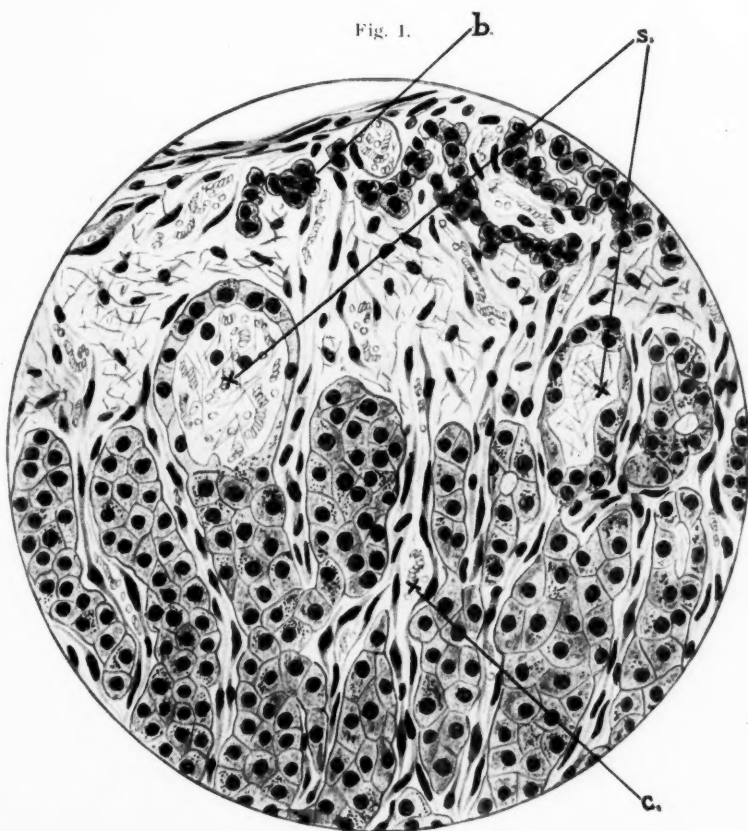


FIG. 2.

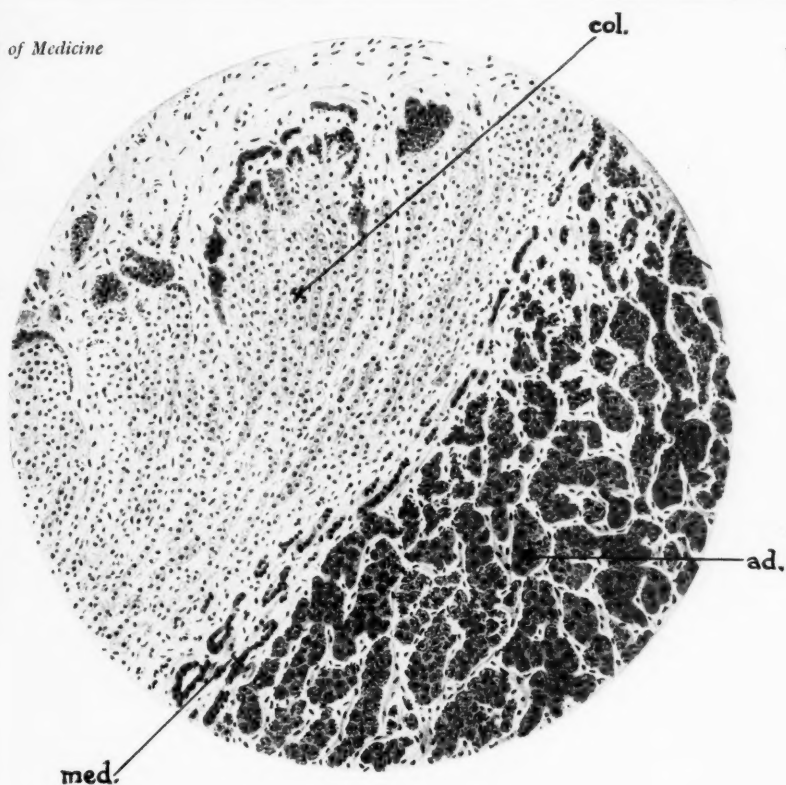


FIG. 3.

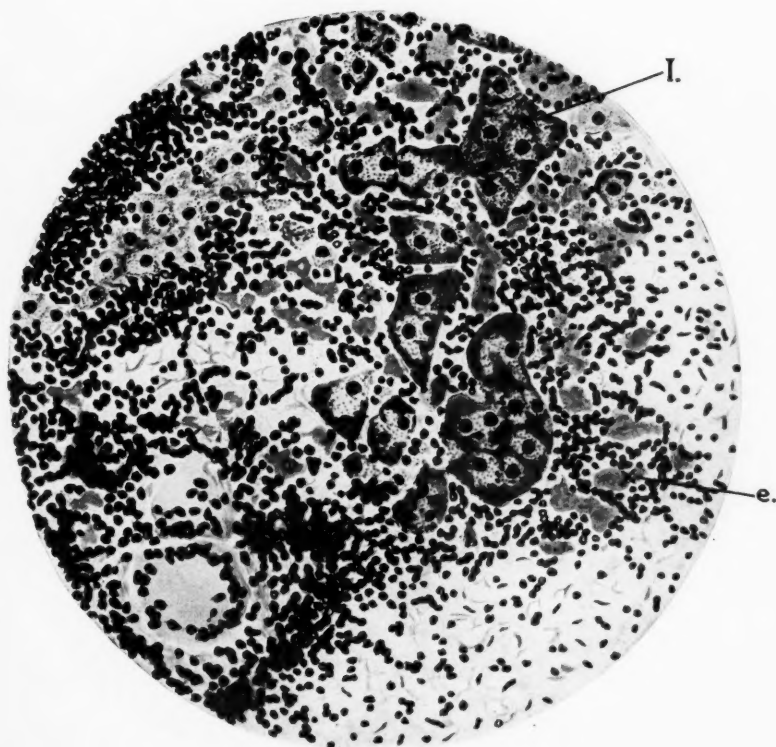


FIG. 4.

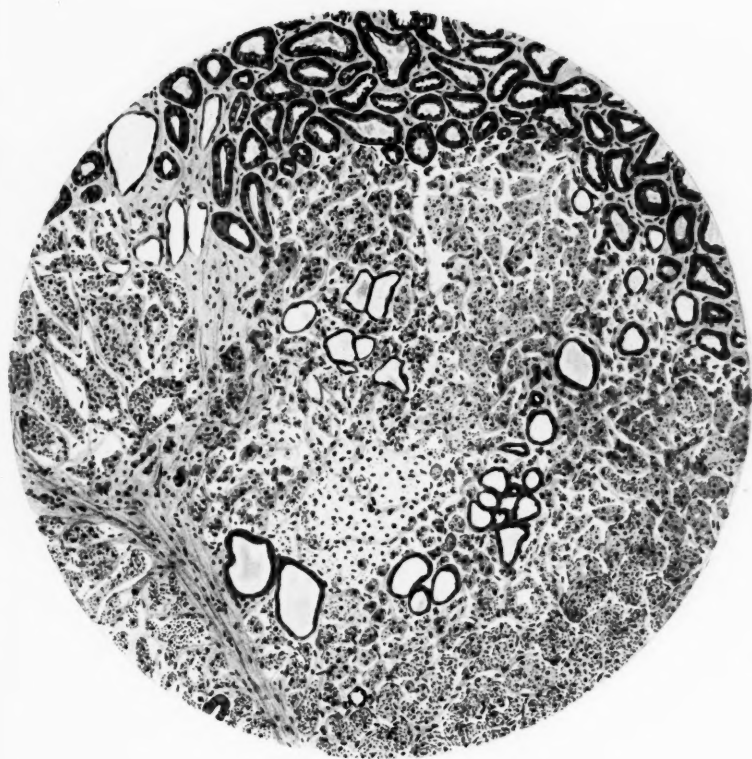


FIG. 5.



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THE TONICITY OF THE ABDOMINAL MUSCLES IN ENTERIC FEVER

By ADAM PATRICK

THE accounts given by the writers on enteric fever of the abdominal symptoms refer chiefly to the presence or absence of pain, tenderness, gurgling, or distension. Not much attention has been paid to the state of the abdominal wall. Murchison, after mentioning the meteorism which, he says, exists in most cases, continues: 'Abdominal pain and tenderness are common, but not necessary symptoms. Patients often complain of pain in the abdomen; and still more frequently tenderness is elicited when pressure is made in the right iliac fossa. I found tenderness at this part in 71 out of 81 cases. . . . Louis noted abdominal pain in 106 out of 127 cases. . . . Jenner noted abdominal pain in 15 out of 20 cases.'

Liebermeister writes: 'Towards the end of the first week, the abdomen is somewhat swollen, tense, and tender on pressure, especially in the ileo-caecal region, in which situation gurgling can be produced by palpation. . . . In the second week, in most cases the tympanitic swelling of the abdomen gradually increases, and towards the end of the second week, from paralysis of the intestinal muscles, there is a considerable degree of meteorismus. The tenderness and gurgling in the ileo-caecal region are more marked.'

In the volume on 'Typhoid and Typhus Fevers' in Nothnagel's *Encyclopaedia of Practical Medicine*, Curschmann and Osler say: 'Abdominal tenderness, spontaneous or on palpation, is rarely present under ordinary conditions. In uncomplicated cases, the patients complain, if at all, of scarcely more than a sense of tension and pressure. Only in the presence of meteorism of marked degree, even if not of inflammatory nature, will palpation often be attended with pain. Far more common than general tenderness in the abdomen is tenderness in the right iliac fossa which is referable to the portion of intestine preferably the seat of the ulcerative process. In some cases this tenderness is constantly somewhat higher towards the liver, and this is possibly due to the congenital dislocation of the caecum upwards (Curschmann), which is known to occur not at all rarely. McCrae has carefully studied 500 cases of typhoid fever at the Johns Hopkins Hospital with reference to abdominal pain and tenderness. He found that about two-fifths of the patients are free from pain or tenderness, rather less than one-fifth have tenderness only. . . . Pain occurred with

haemorrhage or perforation in about 5 per cent. of all cases. It was most constantly present with perforation, where it was usually sudden in onset, severe in character, and paroxysmal in occurrence. In about two-fifths of all cases with pain no cause could be found. In connexion with the question as to whether there is pain associated with an inflamed serous surface over an inflamed Peyer's patch, he quotes an interesting case in which the severe pain, associated with other symptoms, led to a diagnosis of some acute abdominal complication; and an operation was done under local cocaine anaesthesia. Just under the point where the patient had complained of greatest pain was a large Peyer's patch with the serosa much inflamed. With the handling of the intestine he made no complaint of pain, but even a gentle touch over this inflamed area made him cry out. Yet in other cases patients made no complaint when the serous surface over the ulcers was handled. It is questionable whether deep ulceration may be a cause of pain.' According to Ker, 'the abdomen in the vast majority of cases is distinctly tumid. In many cases it is much distended. Tenderness is a frequent symptom, and this may be localized in the right iliac fossa. . . . Pain is occasionally complained of, and may be severe.'

None of these authors speaks of the condition of the muscles of the abdominal wall itself, but two recent writers have made a communication on this subject. Radulesco and Atanassiu say that tenderness over the gall-bladder, with muscular resistance in the right hypochondrium, is an early sign of typhoid infection. Their observations relate to 78 cases in which the diagnosis of enteric fever was confirmed by the Widal reaction. Of 47 patients examined during the first week, every one displayed this sign; in the second week it was present in 65 out of 69 examined; and in the third week, in 23 out of 77. It was encountered in 6 convalescents, and in all of them relapse occurred. The writers think the persistence of this sign into the period of convalescence should convey a warning as to the likelihood of relapse, and that return of the local tenderness after it has disappeared (as it usually does after improvement in the symptoms) is an almost certain premonition of relapse. Its disappearance is an indication of improvement, and warrants a favourable prognosis. Control observations were made on a number of patients suffering from other diseases. Tenderness, with resistance in the right hypochondrium, was encountered in every case of pneumonia (8), and similarly in asystole (15) and right-sided pleurisy (5). In all these cases, however, the pain was a special sensitiveness of the liver, and was not localized over the gall-bladder.

With regard to the condition of the abdomen about to be described, it is of interest to note that it was fully gone into by the late Sir William Gairdner while he still had control of cases of enteric fever. His observations were handed down by two of his pupils of the late 'sixties, and have been studied for a number of years in the City of Glasgow Fever Hospitals. The condition referred to is a slight superficial resistance over a part or the whole of the anterior abdominal wall, with increased superficial resistance in the right hypo-

chondrium. It is due to slight increase in the tonic contraction of the muscles of the abdominal wall, and is to be recognized by light pressure with the fingers. When deeper pressure is made, the resistance is overcome, and is not recognized as long as this pressure is kept up. It is quite different from the deep resistance which is found in cases of general peritonitis, where increase of pressure is met by increase of resistance, and where the state of the parts lying below the abdominal wall is masked by the firm contraction of the abdominal muscles. Where superficial resistance is found, moderate pressure is sufficient to overcome it, and the abdomen can then be palpated almost as easily as the abdomen of a person in health. When the fingers are run lightly over the surface of the abdomen in these cases, the sensation resembles that produced by running the fingers lightly over soft dough. The terms 'doughy' and 'doughiness' were therefore used by Sir William Gairdner in this connexion and seem appropriate.

The superficial resistance is sometimes found over the whole anterior surface of the abdomen, but occurs more usually in a horizontal band with the upper border about 1 inch above the umbilicus, and its lower border 2 or 3 inches below the level of the umbilicus. Sometimes when first observed the resistance is generalized, and afterwards becomes localized in this umbilical belt. If there are variations in the degree of doughiness in different parts, the resistance is more marked on the right side than on the left, and in these cases the middle belly of the right rectus muscle may be slightly prominent. The whole right side may be quite doughy while the left is lax, and it occasionally happens that this right-sided doughiness extends round to the muscles at the back of the abdomen, well behind the right flank.

In association with the superficial resistance of the muscles of the abdominal wall, there is usually found increased resistance in the right hypochondriac region, though either may exist without the other. This resistance is of the same nature as that found in other parts of the abdomen, but is more prominent and lasts longer. Here, too, the resistance can be overcome by moderate pressure, and the parts which lie below examined. The generalized superficial resistance usually passes off in the course of the pyrexia, but that over the gall-bladder lasts longer, and though commonly disappearing about the time the temperature becomes normal, sometimes persists into convalescence.

Tenderness is rarely associated with any of the superficial resistances which have been described.

I made observations on the state of the abdominal muscles in a series of 55 male cases admitted to hospital with enteric fever. Most of these came under notice in the second or the third week of the disease, and I cannot therefore speak of the abdominal condition during the first week. More or less generalized superficial resistance was found in 19 cases at some stage of the disease, usually early, and resistance in a horizontal band in 14 cases. In 11 of these 33 cases there was no accompanying resistance in the right hypochondrium. The degree of superficial resistance seemed to be unconnected with the severity of the attack,

or with the occurrence of diarrhoea or of constipation. One severe case showed a flaccid abdomen throughout pyrexia lasting for fifty-five days, and in some comparatively mild cases doughy muscular resistance was well marked. In ten patients the abdomen was lax throughout the disease.

Of the 55, 32 showed increased resistance in the right hypochondrium, but it was not found, as by the authors quoted, that the condition begins only in the early stages of the disease. It developed later in three patients, in one about the eleventh day, and in two others about the seventeenth. The earliest date on which its disappearance was noted was the fifth before the temperature became normal, and the latest the eighth day of apyrexia. Tenderness was present with the resistance in two only of these cases.

The cause of these abdominal signs is not apparent. It is probable that the superficial resistance is connected in some way with the ulceration of the intestine, while the resistance so commonly found in the right hypochondrium may be associated with ulceration in the ileo-caecal region, which is the part of the intestine most constantly involved.

In this connexion the following case is interesting :

A man, aged 38, was admitted to hospital on the nineteenth day of illness with generalized superficial abdominal resistance, more marked on the right side, and there especially in the right hypochondrium. Considerable toxaemia and some hypostatic congestion in the lungs were present. The pulmonary congestion increased, and the patient became progressively worse until he died on the thirty-fifth day of illness. From the time of admission, however, his abdomen became gradually softer, and on the thirty-second day, three days before death, it was quite lax. At the post-mortem examination all the ulcers were found to be healed. In this case death took place from hypostatic pneumonia, and the disappearance of the superficial resistance in the abdominal muscles seemed to be connected with the healing of the ulcers in the intestine.

It has been suggested that the resistance in the right hypochondrium is due to the infection of the gall-bladder with typhoid bacilli, but against this view is to be urged the fact that the wall of the gall-bladder is not often affected, although the bile is crowded with organisms. As Flexner points out, 'the frequent presence of the bacilli in the bile, and the infrequency of ulceration of the membranes, stand in striking opposition to each other'. It is probable also that the presence of bacilli in the bile much outlasts the muscular resistance. The cause to be sought is one which is in operation approximately as long as the temperature is elevated, and ulceration of the bowel wall suggests itself.

No detailed reference has been made to the muscular resistance which is associated with inflammation of the peritoneum, and which is of quite another kind than that described. It may be found where the floor of an ulcer is thin, and there is slight implication of the peritoneum ; but it is of commonest occurrence when an ulcer has ruptured and generalized peritonitis has commenced. Here the resistance is of the nature of a deep rigidity, pressure of the hand on the abdomen causes pain, and tenderness and rigidity increase with the increase of

pressure. In some cases where rupture seems imminent the rigidity and tenderness gradually pass off as the ulcer heals.

REFERENCES.

- Curschmann (edited by Osler) in 'Typhoid Fever and Typhus Fever' (Nothnagel's *Encyclopaedia of Practical Medicine*), 1902, 213.
Flexner, *Johns Hopkins Hospital Reports*, Baltimore, 1900, viii. 260.
Ker, *Infectious Diseases*, 1909, 252.
Liebermeister in Ziemssen's *Cyclopaedia of the Practice of Medicine*, Lond., 1875, i. 91.
Murchison, *Continued Fevers of Great Britain*, 3rd ed., Lond., 1884, 524.
Radulesco and Atanassiu, *Presse Médicale*, Paris, 1912, xx. 1004.

NOTES OF FURTHER OBSERVATIONS UPON DYSPNOEA AND ITS RELATION TO BLOOD REACTION

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AND

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A Special Symptom-complex.

In a recent communication (1) we have drawn attention to a peculiar symptom-complex associated with reduced alkalinity of the blood occurring in elderly subjects, and comprising:—continuous dyspnoea, often intensified for short periods, especially at night; good or fair blood aeration as judged by the absence of cyanosis, or such cyanosis as would seem compatible with simple cardiac dyspnoea, and by examination of the alveolar air; Cheyne-Stokes breathing with or without full apnoeic periods; an increase of pulse-rate (80–100 per minute); and, lastly, a subnormal temperature. It has also been emphasized that this symptom-complex, associated as it is with cardiac enlargement, general arterial disease, and fibrosis of the kidney in greater or less degree, may be, and frequently is, combined with any of those symptoms spoken of at the present time as uraemic, such for example as temporary hemiplegia or aphasia, vomiting, headache, convulsive seizures or coma; that it may be associated with any form of valvular disease or perverted heart mechanism, and that signs of heart failure are rather the rule than the exception. The view which we have taken is that none of these associations are necessary associations any more than is the high blood pressure or the wasting which are frequent phenomena in such cases, but that they are superadded to a complex which may occur in an almost pure form. We have also drawn attention to the fact that the complex is of extremely frequent occurrence, but that more often than not it is combined with heart failure which veils the condition in greater or lesser degree. Thus considerable cyanosis may be present and the disproportion between the hyperpnoea and lack of blood aeration, the most important clinical sign, may not be distinct. It has been suggested too that in certain of the cases

¹ The expenses connected with these observations have been defrayed partially by a Graham Research Grant, and partially by a grant from the Royal Society.

where Cheyne-Stokes breathing does not appear, the excess of CO_2 in the arterial blood circulating through the respiratory centre may account for its abolition (2). The usual qualities of the urine—low specific gravity, pale colour, increased quantity, which are seen in the less complicated cases—are lost when there is cardio-vascular stasis, and a cardiac urine of high specific gravity, dark in colour, and loaded with urates and phosphates is usually passed in small quantities in its stead. Granular casts and albumin are almost always found. If too the patient is affected by inflammations, and these are by no means uncommon as terminal events, then the temperature is elevated to normal or above the line of normality. A temperature of 98.6° in such patients must be regarded as an evidence of a febrile tendency.

We have emphasized these features because the patients who suffer from acidosis present very diverse clinical pictures, and as a consequence the symptom-complex may not be easy to recognize except in the comparatively rare frank cases, unless the influence of such complications upon the symptom-complex is clearly borne in mind.

Those dyspnoeic patients who are sufferers from a reduced alkalinity of the blood, and in whom the dyspnoea is wholly or largely due to this altered reaction, are placed in different clinical categories, according as some more or less prominent system group or sign impresses itself upon the observer. Thus they pass as cases of renal disease, granular kidney, uraemia, mitral regurgitation, mitral stenosis, aneurism, aortic disease, arterial disease, emphysema, bronchitis, pleurisy, and what not.

In the present series of cases we have not studied the actual reaction of the blood, but the blood 'acidosis', i. e. the excessive acid, exclusive of CO_2 , in the blood as compared with the bases present. Our test, as formerly, was the percentage saturation of the blood with oxygen when exposed at 37°C . to 17 mm. pressure of that gas. For details of the method the reader is referred to our former paper (1) or to Appendix I in *The Respiratory Function of the Blood* (5). The relation between the degree of acidosis and the percentage saturation is tabulated for the observed cases at the end of this paper; here we need only say that the percentage saturation of normal blood, when exposed to 17 mm. pressure, is 75–80 per cent. In proportion as the quantity of acids, relative to bases, is excessive the percentage saturation drops.

We report at the present time four new cases in which the symptomatology is characteristic and relatively uncomplicated (Cases 1–4), and two cases complicated by aortic disease—in one an aneurysm (Cases 5 and 6).

Case 1. Dyspnoea in a man who presented signs of renal and myocardial affections. Nocturnal attacks. Acidosis was found on two occasions.

A. A., a coster of 53 years, was admitted to hospital on account of shortness of breath, palpitation, and aching pain over the praecordium.

History. (8. 11. 13.) He knew of no past illness, with the exception of abscesses in the groin twelve months before. Alcohol had been taken in moderation.

Present illness. Nine months before admission he began to suffer from

breathlessness upon exertion. Very soon the condition became worse and his suffering was intensified by attacks of breathlessness at night, waking him from sleep with a feeling of suffocation and lasting from 10 to 30 minutes. Usually there were one or two such attacks each night. Shortly before admission breathlessness became continuous and palpitation and pain over the praecordium were added.

On admission. (8. 11. 13.) The patient, a spare individual, was orthopnoeic and had slight cyanosis of the lips, tongue, cheeks, and ears and fingers (haemoglobin 98 per cent.). The temperature lay usually at 98°, falling often to 97°. His breathing was hurried, 44 per minute, but being shallow, was accompanied by little distress. It had a tendency to periodicity of the Cheyne-Stokes type. He could hold his breath some nine or more seconds; thus showing some reserve. The heart's dullness lay $1\frac{1}{2}$ and $4\frac{3}{4}$ inches from the mid-line and the third rib. The apex beat was not perceptible; the heart sounds were natural but a little fast; the pulse-rate varied between 98 and 128 per minute from time to time. The mechanism of the heart was normal. The arteries were thickened, the veins were full and freely pulsating. The liver presented some enlargement. Dropsy of the legs and sacrum was present in slight degree. The chest was rigid. There were signs of hydrothorax on the left side, and signs of emphysema and bronchitis over the right chest. The urine, of which some 1,100–1,300 c.c. were voided daily, was of low sp. gr., and contained a faint trace of albumin and many granular casts. An examination of the blood exposed to 18 mm. oxygen pressure gave saturations of 66 per cent. and 67 per cent.

(28. 11. 13.) Seen three weeks later, Cheyne-Stokes breathing had definitely developed, and the nocturnal attacks were a little more frequent. Otherwise his condition remained unaltered. The blood when again tested gave a saturation of 66 per cent.

Case 2. A case of cardio-vascular affection. Dyspnoea on exertion and nocturnal angina pectoris. Acidosis found.

J. L., a caretaker of 47 years, was admitted on 16. 6. 13, complaining of breathlessness, bleeding from the nose, and pain across the chest.

History. At 19 he had rheumatic fever, at 27 syphilis, and at 45 pleurisy.

Present illness. Two months before admission he experienced breathlessness on exertion which increased and became practically continuous, with nocturnal exacerbations which wakened him from sleep. The pain had been severe, coming on from time to time in sudden attacks and shooting across his chest. Shakiness was frequently experienced. Micturition had been frequent, inconveniencing him at night.

Condition. (16. 6. 13.) The patient was a little breathless sitting up in bed or lying on high pillows; the respiratory rate was 24 per minute, the pulse 76–100. Temperature usually one degree below normal. He had no cyanosis. The heart's dullness did not appear to be increased; the heart's mechanism and sounds were normal. The blood pressure was variable between 138–200 mm. Hg. Over the lungs universal rhonchi were heard. The urine was increased in quantity; sp. gr. 1.020–30; no pus, blood or albumin. There was no oedema or signs of venous stasis (Hb. 94 per cent.).

Course. The course was slightly towards improvement on 30. 6. 13. Respirations irregular, rate 16 to 19; orthopnoea slight, very little reserve, night attacks still present from time to time. Cheyne-Stokes breathing was not seen. He had very slight cyanosis of the lips but none of the tongue and fingers. The blood chlorides were increased (Dr. Cotton) to 6.07 grm. per litre, indicating some retention; the blood area was estimated at 0.35 grm. per litre. Exposed to 17 mm. oxygen at 37° C. the blood gave a saturation of 61 per cent.

(16. 5. 14.) The patient has since been attending the Out-patient Department and, passing a life of inactivity, his condition has remained unchanged.

Case 3. A case of arterio-sclerosis and renal affection in a woman who exhibited breathlessness. Nocturnal attacks and Cheyne-Stokes breathing present. Acidosis found.

Mrs. G. (26. 11. 13.) This patient, a woman of 62, was seen on a single occasion. There was no history of past illness but of dyspnoea with frequent nocturnal attacks and intermittent swelling of the legs for three years.

Condition. The heart was not materially enlarged, there were no murmurs. The mechanism was normal; rate 96-112 per minute. The arteries were tortuous and thickened; S.B.P. 160 mm. Hg. The veins were full, the liver large. Dropsy of the legs was considerable. There was slight cyanosis of lips, tongue, and fingers (Hb. 108 per cent.). The respirations were rapid and distressed (42 per minute) during the hyperpnoeic period, which lasted 7 seconds. The apnoeic period was of similar duration. The urine was abundant and contained albumin and abundant granular and hyaline casts. The temperature varied between 98° and 99°. The blood gave a saturation of 64 per cent. to 67 per cent. when exposed to 17 mm. oxygen pressure.

Case 4. A case of cardio-renal affection in an old woman. Cheyne-Stokes breathing and dyspnoea prominent.

Mrs. F., a wasted woman of 77 years, was seen on a single occasion (3. 12. 13). There was a six months' history of breathlessness and no past history of other illness. The patient was orthopnoeic, presented very slight cyanosis of ears, lips, and tongue (haemoglobin 100 per cent.). The temperature was 97°. The pupils were pin-point, reacting sluggishly to light, and the knee-jerks were not obtainable. The heart's dullness was increased, a systolic apical murmur was present, the auricles were fibrillating (ventricular rate 88 to 112 per minute). The arteries were considerably thickened; S.B.P. 130 mm. Hg. The respirations were moderately deep, rate 30-50 per minute and periodic (hyperpnoeic period 67 seconds, apnoeic period 26 seconds). There was not a great deal of distress; the breath could be held for a few seconds during the hyperpnoeic period. The chest was rigid and a few bronchitic signs were present. The veins were distended and showed pulsation; the liver was distinctly enlarged; slight oedema was present over the shins.

The blood gave saturations of 55 per cent. and 56 per cent.

Case 5. Aortic disease and aneurysm, cardiac failure, renal involvement. Dyspnoea, often intensified for short periods, was a chief feature of the case. Cheyne-Stokes breathing was found.

T. E., a carpenter of 44 years, was admitted to hospital on 19. 9. 13 complaining of shortness of breath, swelling of the feet, and palpitation.

History. (19. 9. 13.) At 19 years he acquired syphilis; at 30 years 'Mediterranean Fever'.

Present illness. For 5 years he had suffered from shortness of breath, most conspicuous on exertion, and more recently constant and occurring in intensified paroxysms which wakened him often each night. The sleep was very broken.

On admission. (19. 9. 13.) The patient was orthopnoeic, the respirations rapid (28 per minute); the breathing laboured and periodic (Cheyne-Stokes type). The face was pallid (haemoglobin 98 per cent.). Temperature 96-98°. The arteries were thickened and tortuous; the S.B.P. varied between 150-170 mm. Hg; water-hammer pulse. The heart's mechanism was normal; rate 76-108 per minute. The visible pulsation and area of dullness were notably increased. A systolic murmur and gallop rhythm were audible at the apex, and a coarse to and fro murmur at the aortic cartilage was heard. There was a large area of dullness over the manubrium and upper ribs, and a skiagram showed the outline of a large pulsating tumour. The veins were engorged; the liver was greatly enlarged, ascites was present and a right pleural effusion. The legs and

lower trunk were dropsical. The *urine*, sp. gr. 1.025; cloud of albumin; granular casts; quantity 150–3,150 c.c. per diem.

Course. On 1. 10. 13, four pints of fluid were removed from the chest and he obtained a little relief. On 2. 10. 13, the condition showed some improvement; the dropsy had declined. The respiratory rate was 36 per minute during the hyperpnoeic periods; these lasted each about 50 seconds and were followed by apnoeic periods of 10 to 20 seconds. Distress was still considerable. Very slight cyanosis was seen in the lips, tongue, ears, and fingers. The veins and liver were engorged as before, and there were general bronchitic signs. Examination of the blood gave 60 per cent. saturation. Later the oedema increased, necessitating drainage, and vomiting appeared; the patient sank gradually and died on 14. 11. 13.

Post-mortem. The body showed considerable anasarca and fluid in all the cavities. The heart weighed 877 grm. (vent. muscle, 563 grm.; R. = 135, L. = 362, and septum = 66). The aortic valves were crumpled and incompetent. The cavities were dilated, the coronaries patent and wide but very calcareous. A large sacculated aneurysm was found upon the arch of the aorta. The liver was of nutmeg type, the spleen firm and congested. The *kidneys* weighed 170 grammes apiece; they were tough and congested, but the surfaces were smooth and the capsules stripped easily. In the *lungs* patches of collapse were found.

Case 6. A case of aortic disease, cardiac failure, and renal involvement. Dyspnoea, Cheyne-Stokes breathing, nocturnal intensification of breathlessness, prominent. Terminal pneumonia present.

G. G., a caretaker of 42 years, admitted to hospital complaining of shortness of breath, pain in left shoulder and chest.

History. He had suffered from rheumatic fever and pneumonia at 18 years.

Present illness. (18. 11. 13.) Shortness of breath, especially upon exertion, had been present for two years. At night he was often awakened, and sometimes repeatedly, by severe breathlessness, lasting a quarter to half an hour. Before admission the breathlessness and pain had been continual.

On admission. (18. 11. 13.) The patient was orthopnoeic, the breathing laboured (rate 40 per minute). Cheyne-Stokes breathing was present (hyperpnoeic period 40 seconds, apnoeic 10 seconds). His face was pallid (haemoglobin 78 per cent.). He had slight cyanosis of cheeks and ears, lips, and tongue. The breath had a sweet ethereal smell. The temperature was 100.8°. The heart's action was rapid (pulse 128 per minute); its mechanism normal; the area of dullness and pulsation being greatly increased; a systolic murmur was audible at the apex, and rough to and fro murmurs at the aortic area. The arteries were thickened; S. B. P. 126 mm. Hg; water-hammer pulse. Veins full and pulsating. The liver greatly distended. No oedema or ascites. The *urine* was decreased in quantity (250–1,100 c.c.) and of high colour; sp. gr. 1.030, and contained a cloud of albumin and granular casts. The *lungs*: there was profuse sputum, which was blood-stained. The chest was hyper-resonant; the breath sounds harsh. A little impairment of note was discovered at the right apex; râles and rhonchi were universal.

A positive Wassermann reaction was discovered. The blood exposed to oxygen gave saturations of 46 per cent. and 52 per cent.

Course. The temperature fluctuated between 97.5° and 102°; he became weaker and delirious, dying on the 22nd.

Post-mortem. Fluid was found in both pleurae, the bases of the *lungs* were in a state of red hepatization. The heart weighed 632 grm. (muscle, 416.5 grm.; R. 129, L. 241, and septum 46.4 grm.). The aortic valves were crumpled and retracted, regurgitation having been free. The mitral and tricuspid rings and the heart chambers were dilated. The orifices of the coronary

vessels were a little narrow, but the vessels were healthy. The *kidneys* weighed 242 grm. apiece; they were congested; the capsules a little thickened. The epithelium was swollen and granular; little or no fibrosis; intimal thickening of the vessels. The liver was enlarged and nutmeg. The spleen was swollen and its capsule thickened.

Simple Cardiac Dyspnoea.

In our first report we gave the details of examination in three cases of heart disease in which there was no acidosis, and in which the breathlessness could be attributed solely to deficient aeration of the blood. At the present time, we add three similar cases to the list (Cases 7, 8, and 9) of those in which no acidosis was discovered.

Case 7. Cardiac failure of rheumatic or specific origin, in a man who exhibited mitral stenosis and aortic disease. Dyspnoea present. No acidosis.

G. W., a man of 35 years, was admitted with symptoms and signs of cardiac failure on 10.10.13.

History. Syphilis at 21 years; rheumatic fever at 23 years of age.

Present illness. Shortness of breath on exertion or at rest, and swelling of legs, of one year's duration, frequent headaches and sleeplessness were the chief symptoms.

Condition. (11.10.13.) An orthopnoic patient of high colour (Hb. 104 per cent.) who presented some cyanosis. The breathing was shallow and 28 per minute. The veins and liver were engorged. No ascites, but moderate dropsy of legs and signs of oedema at lung bases. The heart enlarged, free aortic regurgitation; a full diastolic rumble at the apex and blowing systolic murmur. Auricular fibrillation (heart rate 100). Temperature 97-98°. Blood pressure 96-100 mm. Hg. *Urine* dark, sp. gr. 1,030, scanty, containing urates and albumin.

Course. (2.11.13.) He could lie flat without much discomfort, but the breathing became increased in rate. While propped up the rate was 28 and regular; there was no distress; he had some reserve, the breath being held 15 seconds, but it was incomplete. He had had attacks of nocturnal breathlessness but was at the time free from them. There was slight cyanosis of lips and very slight of ears and tongue. The engorgement of veins and liver had gone, as had the dropsy. The blood exposed to 17 mm. oxygen pressure gave a saturation of 77 per cent.

Case 8. A case of mitral stenosis with auricular fibrillation and cardiac failure. No acidosis found.

Mrs. S., a woman of 28 years, was admitted on 10.6.13, complaining of pain in the abdomen and shortness of breath.

History. Rheumatic fever at 20 years.

Present illness. Pain had been present over the upper abdomen and she had had shortness of breath for two years. The symptoms had recently become more urgent. Colour high (haemoglobin 90 per cent.).

Condition. (11.6.13.) The patient was orthopnoic, but while sitting there was but little dyspnoea (rate 23 per minute, respirations irregular). A little cyanosis. The heart was enlarged and showed clear signs of mitral stenosis and fibrillation. Arteries normal; S. B. P. 126-136 mm. Hg. The liver considerably enlarged. The veins full. No ascites or oedema. Spleen palpable. The *urine* contained a trace of albumin; quantity 400-1,350 c.c. per diem; sp. gr. 1,030-1,019. Temperature normal.

Course. (30.6.13.) Orthopnoea still present. A little dyspnoea (rate 20-24,

a little laboured); she had a good deal of reserve, holding the breath 20 seconds, but it was by no means complete. Slight cyanosis present in lips, tongue, cheeks, and ears. Blood chlorides 5.74 and urea 0.33 grm. per litre (Dr. Cotton). The blood exposed to 17 mm. oxygen pressure gave a saturation of 74 per cent.

Case 9. Cardiac failure in a patient who exhibited mitral stenosis. Dyspnoea present, but no acidosis.

Mrs. A., a woman of 26, was admitted to hospital complaining of breathlessness and swelling of the legs.

History. There was no history of past illness, with the exception of bronchitis, developed sixteen months before and leading up to the illness for which she was admitted.

Condition. (2.11.13.) Seen on a single occasion, she was orthopnoeic, and gave a history of nocturnal attacks of breathlessness, the result of slipping down the bed off her pillows. She was flushed (Hb. 90 per cent.) and showed slight cyanosis of lips and cheeks, but none of the ears and fingers. Respirations were at 25 per minute, regular and deep but not distressed; of reserve there was little or none. The heart was enlarged, and clear signs of mitral stenosis were present; its mechanism was normal, the pulse being 108-128. The arteries seemed normal; S. B. P. 100 mm. Hg. The veins were a little full but did not pulsate freely; the liver showed conspicuous enlargement. She had dropsy of the legs and body wall. The urine varied in quantity from 390 to 1,300 c.c. per diem, and contained a trace of albumin and hyaline casts. Over the lungs there were universal signs of bronchitis. The temperature lay between 97° and 98° as a rule. The blood exposed to oxygen gave a saturation of 77 per cent.

Speaking with these cases and those of our previous report in view, it seems to us that from the point of view of blood reaction and dyspnoea, cases of heart disease may be divided into two classes. There are the relatively simple and uncomplicated cases, where, though failure may be present originally, recovery is the rule. These are usually young subjects with fresh or heightened colour, and although cyanosis, slight, moderate, or deep, is present, dyspnoea, as indicated by the rate of respiration, is not great. The respirations range from 25 to 35 per minute, orthopnoea is present, and the field of respiratory response is strictly limited. In these patients no acidosis is found.

Young patients affected by mitral stenosis do not present reduced blood alkalinity in our experience, unless the condition is complicated. It is quite apparent from our observations that acidosis is a frequent accompaniment of heart failure, especially in middle-aged or elderly subjects, and *a fortiori* in chronic or terminal heart failure. But that heart failure with signs of venous engorgement and oedema of the legs may occur apart from this intoxication is equally clear. The acidosis cannot be attributed to heart failure alone, and we turn naturally to the excretory organs in seeking its explanation.

The prevalence of reduced alkalinity of the blood in heart patients may be judged from the statement that the majority of those patients who are persistently distressed for want of breath, and who, with muddy and sunken countenances, sit in our wards and exhibit the classical signs of heart failure, be they patients who gradually sink and die, or be they patients who are temporarily relieved, are sufferers from the condition considered.

The Renal Factor.

It has been stated in our previous report that those cases of heart disease which have shown acidosis have also presented signs of renal involvement, clinical or *post mortem*. The extent to which the acidosis may be attributed to a renal factor has been discussed by us, and we have avoided a final decision, as in our reports we have also avoided the use of the term uraemic. Although many of our patients would unquestionably be termed by many observers uraemic or uraemic asthmatics, the application of such terms to them is evidently fraught with danger. The terms presuppose the origin of the dyspnoea in a renal lesion; ultimately it may or may not be found to result from such.

To tabulate patients in whom reduced alkalinity has been found under the heading of uraemia, even though Straub and Schlayer (4) and others (3) have found evidence of this condition of the blood in cases diagnosed as uraemic from other signs, is to perpetuate a suggestion for which there is neither proof nor disproof, namely, that such reduced alkalinity is of renal origin. The safer policy at the present stage of the investigation is fully to report the facts on the clinical side, leaving the ultimate solution and the final clinical grouping to a time when our observations are more complete.

That there is very suggestive evidence of a metabolic disorder of renal origin is true, and two cases which we have recently observed would seem to strongly support such a contention (Cases 10 and 11).

Case 10. Pregnancy in a patient suffering from rheumatic heart disease. Breathlessness accompanied by acidosis.

M. B., a woman of 23 years, was admitted to hospital on 5. 6. 14.

History. At 20 the patient had rheumatic fever.

Present illness. For seven months there had been increasing difficulty in mounting stairs, on account of breathlessness. For two months the breathing had been more difficult, preventing her sleeping except in a chair or with many pillows. Morning vomiting had distressed her for two months, and she had suffered from cough with blood-stained expectoration for the same period.

Condition. (8. 6. 14.) A cheery and well-nourished primigravida, daily expecting confinement. She was orthopnoeic; the respiratory rate was 44, but the breathing shallow. The colour was good, a little cyanosis only being present in the lips. She was able to hold the breath five seconds, but deep breathing was followed by no trace of apnoea. The temperature was usually subnormal (97-99°). The heart was somewhat enlarged; a thrill was present at the apex, and other evident signs of mitral stenosis accompanied it. The mechanism was normal but for occasional extra-systoles. The pulse-rate was 88 per minute. Oedema of the legs and sacrum was present. The veins were a little full; enlargement of the liver could not be detected. S. B. P. 108-125 mm. Hg. The urine varied in quantity from 150 to 1,400 c.c. per diem, being usually about 500 c.c.; sp. gr. 1,013-1,030; albumin and granular casts present. The lungs: beyond a little basic dullness with a few crepitations the lungs and pleurae seemed normal. The blood exposed to oxygen showed *acidosis*, but its actual degree was uncertain but considerable, corresponding to a degree indicated by something of the order of 45 per cent. saturation for an exposure of the blood to 17 mm. oxygen.

(15. 6. 14.) By this date the condition had improved. Breathlessness was less, but still present; the respirations being 32 per minute; the breath could be

held five seconds and deep breathing produced no apnoea. There was no cyanosis and the dropsy had decreased a good deal. The pulse-rate was 76. The blood exposed to oxygen gave saturations of 53 per cent. and 57 per cent.

(16. 6. 14.) The patient was delivered of a full-term child without accident.

(22. 6. 14.) There was much improvement. The pillows had been removed; the respiratory rate had fallen to 26; the breath could be held fifteen seconds. The colour was fresh and the patient comfortable.

The chief interest of this case of mitral stenosis is its associated pregnancy. It suggests to us that eclamptic breathlessness may be of acid origin. Other cases of the same valve affection, in which renal lesions were discovered at autopsy and in which breathlessness was largely attributable to altered blood reaction, have been recorded previously.

Case 11. A case of large white kidney, with dropsy of renal type, complicated by aortic disease and slight mitral stenosis. Urgent breathlessness in the absence of cyanosis was a feature of the case. Acidosis was discovered.

J. N., a man of 37 years, was admitted to hospital complaining of anaemia, swelling of the body, and breathlessness.

History. (24. 10. 13.) There was no history of past illness or of alcoholism.

Present illness. In April, 1912, the patient began to develop puffiness of the eyelids, and a little later swelling of the scrotum, arms, and legs. He had been failing in strength for some time previously. At the same time he noticed that he was becoming paler and that he could not exert himself without becoming breathless. Shortly before admission his breathlessness was more conspicuous towards and during the night, preventing him from sleeping or waking him repeatedly. He suffered from nausea but had no vomiting.

On admission. (24. 10. 13.) The patient lay propped with pillows. He was very pale (haemoglobin 50 per cent.) but exhibited no trace of cyanosis. He had universal oedema of the boggy type. The eyelids, cheeks, and conjunctivae were dropsical; the arms were enormously infiltrated with fluid; so too were the lips, genitalia, and body wall. There were signs of pleural effusions and of a collection of ascitic fluid. The temperature showed variations between 97.5° and 101°. Respirations were very laboured at a rate of 36 per minute; there was no reserve of breathing, the respirations were regular. The breathing was more hurried, so it was stated, at night, and the distress of the patient great. Cheyne-Stokes breathing was not seen at this or any other time. The heart presented signs of enlargement; its action was regular at 118-120 per minute. A systolic murmur was audible over the epigastrium. The blood pressure, obtained after gradually squeezing the tissues of the raised arm free of oedema, was measured at 160 mm. Hg. The brachial artery in this arm seemed thickened. There was no appreciable engorgement of the veins; the liver showed no sign of engorgement. The urine had a sp. gr. of 1.020, and contained abundant albumin, a good deal of blood (foggy or coloured), and granular casts; the quantity varied from 370 to 780 c.c. daily. Examination of the blood gave saturations of 43.5 and 44 per cent. Death occurred on the 29th of the same month.

Post-mortem. Universal oedema, great ascites, and large pleural effusions were discovered. The aorta was healthy, the peripheral vessels atheromatous. The pericardium was universally adherent by tissue which readily broke down. The heart weighed 747 grm., the muscle of the ventricles weighed 423.5 grm. (R. V. 112; L. V. 243; septum 68.5). The coronary arteries were normal; no clots were found in the cavities. The aortic valves were a little crumpled at

their margins and slightly incompetent; at their bases they were calcareous. An old-standing abscess, a centimetre in diameter and having thick fibrous walls, was discovered between aorta and pulmonary artery immediately above the valves. The mitral valves were thickened and the orifice narrowed to 260 sq. mm. The *liver* weighed 1,760 gm. and was fatty and congested; the *spleen* weighed 277 gm.; the capsule was thick, the substance pale and friable. The *lungs* presented patches of collapse and emphysema; small infarcts were found in both. The *kidneys* were large (341 gm.) and pale. The surfaces were smooth, the capsules stripped easily. The cortex was broad, the Malpighian corpuscles prominent; the substance of the organ was firm. Histologically, the organs demonstrated a chronic parenchymatous nephritis with diffuse interstitial change. The nuclei of the Malpighian corpuscles had proliferated: no hyaline corpuscles were seen. There was a good deal of interstitial fibrosis and lymphocytosis, and some intimal thickening of the vessels.

The second case (Case 11) is of importance because it is the first of our series in which the nephritis was of a conspicuous parenchymatous type. Clinically this man appeared to be a characteristic instance of the large white kidney; the universal dropsy of frank renal type, and the character of the urine, pointed clearly to gross renal insufficiency; yet at the post-mortem unsuspected aortic and mitral lesions, inconspicuous it is true, were discovered. It seems to us that observations are still required upon instances of a still purer kind, namely, upon those in whom renal lesions are the sole gross or manifest affections, before we can finally state that dyspnoea of purely renal origin exists. That renal dyspnoea so called is the result of reduced blood alkalinity we see no reason to doubt; but that is an entirely different statement, for the term uraemic is comprehensive and is applied clinically to a variety of conditions, the exact nature of which is still unknown. We require also chemical investigation as well to give us a clear insight into the actual metabolic changes occurring in the body.

Certain it is that in the cases of acidosis which we describe we have to deal with a changed metabolism as profound in its symptomatic effects as is the altered metabolism of diabetes, and of far greater consequence than the latter, because so much commoner.

A Note upon Mechanical Dyspnoea.

To refer dyspnoea entirely and solely to mechanical causes when we have clear evidence of a lesion which is known oftentimes to obstruct the respiratory passages, or where we are certain that a large proportion of the lung tissue is out of action, or when deficiencies of the pulmonary circulation are suspected, is a temptation to which we yield only too naturally. But it appears that our reasoning is not always to be justified; we have reported, for example, an instance of aneurysm in which continuous dyspnoea, often exaggerated, might have aroused the facile explanation of obstructive dyspnoea from pressure on trachea or bronchus. That such was not the main cause is shown by the blood analysis. Our next case may be used as an even more notable example of the same point of view (Case 12).

Case 12. Pneumothorax giving rise to acute illness in a dormant case of pulmonary tuberculosis. Dyspnoea accounted for, partially at all events, by acidosis.

F. P., a police officer of 25 years, was admitted to hospital on 27.4.14 acutely ill.

History. The only past illness was a history of early tuberculosis for which the patient was treated in a sanatorium from July to December, 1913. His acute illness started the day before admission with fever and breathlessness.

Condition. (27.4.14.) The patient, a well-developed man, lay in bed. The skin was hot, the face flushed (Hb. 98 per cent.). He had very slight cyanosis, but a good deal of dyspnoea. The temperature was 103.4°, the pulse 128, and respirations 40 per minute. There was some mental confusion. Weak breath sounds and dullness to percussion were discovered in the left axilla. The heart limits and sounds were normal. The patient was considered to be suffering from acute pneumonia.

Course. On 29.4.14 the temperature remained unchanged. A slight herpetic eruption had appeared upon the chin. Breathing was less hurried. The respiratory rate at the time of examination was 24, though respirations were deep and the alae nasi were working. The colour was high; slight cyanosis being also present in the lips. A blood examination showed no acidosis, the percentage saturation being 75 per cent. Pneumococci were abundant in the sputum, which was frothy, but no tubercle bacillus could be found. On 1.5.14 the heart's dullness was first missed, and by the 7th it was perfectly evident that the patient had developed hydropneumothorax (Bell sound and subsequent radiograms). At examination on 4.5.14, the temperature was 101.6°, respirations 42, and the pulse 180. The patient's distress had increased, though there was little cyanosis. Blood examinations gave saturations of 52 per cent. and 60 per cent. On the 7th, sixteen ounces of turbid sero-fibrinous fluid were drawn from the left pleura; it contained numerous polymorph leucocytes, but no organisms (tubercle bacilli ultimately discovered in inoculated guinea-pig). From this date he improved considerably, the temperature falling gradually to normal on May 18. On this day the pulse was 78; the respiratory rate had fallen abnormally low, being 12 per minute. The patient had recovered his respiratory reserve. Blood examination gave saturations of 77 per cent. and 79 per cent.

In a patient who has breathlessness and clear signs of collapse of one lung, the hyperpnoea proves to be wholly or in part due to acid intoxication. Observations of this kind show only too clearly how dyspnoea of toxic origin may be interpreted erroneously upon purely physical lines, and awaken considerable distrust of mechanical explanations as they are commonly applied in individual cases.

In exophthalmic goitre breathlessness is not uncommon; where there is serious embarrassment, an enlarged thyroid or thymus gland is often held responsible. The following case (Case 13) shows that breathlessness may be due to a third cause, namely, altered blood reaction:

Case 13. A case of exophthalmic goitre, complicated by maniacal symptoms, persistent vomiting, and distress of breathing in a young man. Acidosis was found. Death from exhaustion.

A. L., a market stall-keeper of 30 years, was admitted complaining of pain in the pericardial region and difficulty in breathing.

History. (9.12.13.) With the exception of a temporary cough and blood-spitting, three years before, he knew of no illness.

Present illness. Two years before admission he had first noticed tremor of the hands and swelling and roundness of the neck. A little later, pain over the heart and difficulty in breathing were observed. Six months before admission the eyes became prominent. Headache, beating in the neck, and sleeplessness have disturbed him; the most recent symptom had been diarrhoea.

Condition. (9. 12. 13.) The patient was very dyspnoeic, respirations 46 per minute, and distressed. The colour was natural (blood counts normal); the skin moist. He had characteristic signs of exophthalmic goitre. The thyroid was enlarged uniformly, the neck pulsated freely and exhibited a systolic thrill. The hands and fingers were tremulous; the eyeballs prominent; von Graefe's sign present. The pulse was 138; the S.B.P. 128-140; the action of the heart was regular. The heart's impulse was forcible, but the dullness was not increased. The lungs presented no physical signs. *Urine* normal. There were no further signs of involvement of the nervous system.

Course. During his illness the temperature was normal. He had persistent vomiting of an intractable type and suffered greatly from sleeplessness. The breathing was not embarrassed to a constant extent, but being always difficult, it became urgently laboured in attacks lasting a few minutes or half an hour. On 15. 12. 13 the breathing was rapid and shallow, but showed some reserve; he had slight orthopnoea; forced breathing was followed by no period of apnoea but by hurried respirations. The blood exposed to oxygen gave saturations of 52 per cent. and 56 per cent. Alveolar air samples contained 5.4 and 4.6 per cent. CO₂ (estimation of K, 0.00018).

The patient developed maniacal symptoms, dyspnoea and vomiting continuing, and he died from exhaustion (18. 12. 13).

That the acidosis of this case was of the same nature as that discovered in cardio-renal patients seems to us improbable; we have made no further attempt to identify the actual error of metabolism, being content at present to record an alteration of blood reaction originating in the presence of a non-volatile acid.

Pneumonia.

In one of our cardio-renal cases (Case 6), pneumonic consolidation of the lungs was found at autopsy; it was considered advisable to control this case by observations upon simple pneumonic patients; more especially as the degree of dyspnoea often appears to be in excess of the cyanosis in this malady.

We include reports of four cases (Cases 14, 15, 16, and 17), in each of which a non-volatile acidosis was discovered. The acidosis of pneumonia is present during the febrile stage of the disease (Case 14) and remains for some while after the crisis, disappearing hand in hand with the breathlessness during convalescence. It may be of considerable degree (Cases 15 and 16); in two patients in whom the oxygen saturation fell to or below 40 per cent., the termination was fatal. Further observations should determine the diagnostic significance of the blood reaction in these cases, and may possibly show it to be of prognostic significance.

That acute pneumonic infection may be responsible for an altered blood reaction suggests that we should inquire further into the cause of dyspnoea in such conditions as septicaemia, infective endocarditis, &c.; for it may be that similar changes will be found in these patients also.

Case 14. A case of acute pneumonia in a young man, ending in recovery. On the fourth day acidosis was found. The crisis occurred on the eighth day; acidosis, though of lesser degree, was present on the tenth day; during convalescence the blood reaction was normal.

T. D., aged 27, a beer drinker, was admitted to hospital on 22. 12. 13, complaining of vomiting, headache, and pain in the right side of his chest.

History. (22. 12. 13.) He had pneumonia 7 years ago. Alcohol consumption free.

Present illness. On Saturday, the 20th, he was at work and well; on Sunday afternoon, the 21st, he felt chilled, and in the evening malaise and shivering were experienced. Pain in the right side, headache, and vomiting developed.

On admission. (22. 12. 13.) A robust man who lay a little propped in bed. The mucous membranes were of healthy colour. The breathing was hurried, 28 to 30 per minute; the temperature 98.8° . He had herpes of lips and nose. The *lungs*: the right side of the chest showed limitation of movement, dullness to percussion and prolongation of respiration. The action of the *heart* was rapid, 104 per minute, otherwise this organ seemed normal. The urine was normal.

Course. The temperature rose on the day of admission to 103.4° ; it oscillated over one degree and fell gradually from a maximal of 103.4° to 100.5° on the 28th; from this point it sank abruptly to the normal and subsequently remained at or about normal for the rest of his stay.

(24. 12. 13.) On this, the fourth day of illness, an extensive patch of dullness could be made out, extending from the spine of the scapula to the base; over this area expirations were prolonged. Râles and rhonchi were audible over both bases posteriorly and friction in the axilla. The sputum was rusty. The *heart* was not enlarged (rate 106-112, regular). The S.B.P. was 128 mm. Hg. Venous reservoirs and arteries normal. *Urine*, sp. gr. 1030; contained a trace of albumin, but no casts.

The respirations were 32 per minute, he had little or no distress, the breath could be held for 15 seconds and apnoea followed deep breathing. There was no cyanosis. The blood exposed to 17 mm. oxygen pressure gave saturations of 59 per cent. and 60 per cent.

(28. 12. 13—8th day.) Temperature normal; bronchial or tubular breath sounds over right lung posteriorly; crepitations over both bases.

(30. 12. 13—10th day.) Temperature $97-98^{\circ}$, some delirium. Respiratory rate 24-28 per minute, pulse 76-80 per minute. There was no distress or cyanosis. The signs at the right base were beginning to clear up. *Saturation of blood exposed to oxygen* 67 per cent. From this time onwards improvement was rapid and steady, and by 14. 1. 14 the dullness at the right base had almost vanished.

(26. 1. 14.) There remained a few crepitations at the right base and some increased conduction of respiratory and vocal sounds. The temperature and pulse-rate were normal. He was perfectly comfortable, the respiratory rate being 20 per minute with full reserve. *Saturation of blood exposed to oxygen* 70 per cent. and 72 per cent.

Case 15. A case of severe acute pneumonia in a young man, terminating fatally. Profound acidosis was discovered on the tenth day of illness.

M. G., a clerk of 22 years, was admitted to hospital on 30. 5. 14, complaining of shortness of breath and pains over the whole chest.

History. (3. 6. 14.) As a young child he had whooping-cough, measles, and

pneumonia. At 11 and 12 years he had rheumatic fever and at 16 years pleurisy. He had taken no alcohol.

Present illness. His symptoms developed suddenly one week before admission and had gradually increased in severity.

On admission. (30. 5. 14.) He lay propped in bed, the cheeks flushed; the temperature being 103°. Respiration was hurried and distressed, the rate being 44 per minute. There was a little cyanosis. The *lungs*: movement of the chest wall was deficient on the left side, resonance was increased, and bronchial breath sounds were audible at both bases. The sputum was rusty and contained numerous streptococci and pneumococci. The *heart* limits were normal; an occasional soft systolic murmur was audible at the apex. The pulse was regular, the rate being 120 per minute. *Urine*, sp. gr. 1.015; contained a faint cloud of albumin.

Course. The maximal temperature fell gradually to 101° on June 7, fluctuating over two or three degrees.

(2. 6. 14.) Temperature 101.5°; the signs in the lungs were much as before. The pulse-rate was 45 per minute and breathing was laboured. He had practically no cyanosis. He was anxious and tending to delirium. *Saturation of the blood exposed to 17 mm. oxygen pressure 34 per cent.*

By June 7 it was obvious that almost the whole left lung was involved and signs of some consolidation were also present on the right side. The patient was delirious; an exploratory puncture at the left base yielded a small quantity of very blood-stained fluid. Early in the morning of the 8th large quantities of rusty sputum were ejected, the breathing being much embarrassed. He collapsed and died shortly afterwards. A post-mortem was refused.

Case 16. *A case of acute pneumonia, ending fatally, in an elderly woman. Acidosis was found on two occasions during the course of the illness. The CO₂ tension in exposed air was low.*

Mrs. W., a woman of 74 years, was admitted to hospital on 1. 12. 13 complaining of shortness of breath, cough, and pain in the right chest.

Present illness. The illness was of four days' duration; the onset sudden.

On admission. (3. 12. 13.) Seen on the sixth day of the disease, the patient lay in bed, propped with pillows and in some respiratory distress and delirious. There was slight cyanosis of lips, ears, cheeks, and tongue. The temperature was 102.5°. Herpes was present on the lip. The respiratory rate was 36 per minute; there was no reserve. Dullness and crepitations with friction accompanied by weak hollow breath sounds were found in the right axilla and at the base. The sputum was scanty and a little stained. The pulse-rate was 114, the heart being regular. The *heart* showed some increase in size; mitral regurgitation was present. The arteries were thickened. The blood exposed to 17 mm. oxygen pressure gave saturations of 49 per cent. and 53 per cent.

Course. The temperature remained high and irregular (99–103.5°) until she was seen again on 10. 12. 13. The physical signs were then found to be practically unaltered, though the patient was weaker. The respirations were still 36 per minute, though perhaps less laboured than before. The pulse-rate was 126 per minute; there was no cyanosis. The blood gave a saturation of 66 per cent. Collected samples of expired air contained 3.0 and 3.3 per cent. CO₂. The patient died on the 11th, a post-mortem investigation being refused.

Case 17. *A case of acute lobar pneumonia in an otherwise healthy young man; ending in recovery. Acidosis was found.*

W. H., a clerk of 22 years, was admitted to hospital (25. 12. 13) complaining of pain in the left chest, dizziness, sickness, and weakness of two days' duration.

History. (25. 12. 13.) Habits temperate. No past illness of consequence.

Present illness. His illness commenced acutely on the 23rd with the above-mentioned symptoms.

Condition. (25.12.13.) The patient lay propped in bed, was dyspnoeic and weak, the face flushed and the skin dry. The temperature 103–105°, the respirations 34, and the pulse 106 per minute. The heart showed no sign of enlargement, its action was rapid but regular, the sounds were normal. S.B.P. 111–120 per minute. The *urine* was high coloured, but otherwise normal. *Lungs:* there was limitation of movement and dullness to percussion in the left axilla and behind over the whole lower lobe; at the top of this dull area the breath sounds were harsh, below they were weak or absent. Friction was audible below the angle of the left scapula. The sputum consists of greenish sticky mucus.

Course. The crisis occurred on the evening of 27.12.13; the temperature falling rapidly from 103° to normal and remaining there. On 30.12.13, the respirations were 28 per minute; there was still some distress, but there was no cyanosis and no signs of venous engorgement. A few râles had appeared over the left lower lobe of the lungs. The pulse-rate was 88 per minute. The blood exposed to 17 mm. oxygen pressure gave a *saturation of 54 per cent.* The course was towards rapid and uneventful recovery. Hollow breath sounds were heard over the left lung on 15.1.14, the breathing being easy. On 16.1.14 the patient got up; crepitations were still present but were clearing. He was discharged to a convalescent home on 22.1.14.

Spasmodic dyspnoea.

Lastly, we report a case of exceptional interest; a man who suffered from acute paroxysms of breathlessness of several hours duration (Case 18).

Case 18. Paroxysmal breathlessness in a man who had signs of cardiac and renal involvement with aortic aneurysm. Exaggerated acidosis found during the attack.

J. B., a driver of 50 years, was sent to the Out-patient Department for examination and report by Dr. Sidney Owen.

History. Of past illnesses, he gave a history of gonorrhoea at 25 years, and some 18 months before admission had suffered much from eczema and carbuncles.

Present illness. For 3 months he had suffered from breathlessness, especially upon exertion, and his work had become increasingly difficult. In the middle of June he was sitting in his car on the rank when he noticed himself more breathless than usual. In a few minutes the breathlessness increased so much as almost to suffocate him; he collapsed and became unconscious, was driven to the West London Hospital and admitted. In a few hours the attack subsided entirely, leaving him as he was before it came.

(8.6.14.) When he came to the Out-patient Department his condition was as follows: A strongly-built full-blooded man, with a very faint trace of cyanosis. While talking he was a little breathless, but was able to lie fully prone and at ease. The veins were a little full, the pulse regular and at normal rate. The heart was enlarged, but presented no murmurs. A few crackles were heard at both bases. Without warning, and while sitting on the couch, he began to pant, and within a few minutes he presented a picture which gave rise to anxiety for his life. The breathing was of the most laboured kind, the face quickly became cyanosed and intensely pale, sweat broke out all over him. The cyanosis was definitely of later origin than the urgent breathing. Orthopnoeic,

he literally gasped for air and had the appearance of a cardio-renal patient *in extremis*. The heart's dullness meanwhile showed no increase, but the chest had evidently enlarged and râles and rhonchi appeared universally over it. No sputum was ejected. Oxygen seemed to afford little or no relief; he passed a quantity of limpid (sp. gr. 1,008) urine (stating that he had done likewise in the former attack). An attempted venesection was almost unsuccessful at first; the veins seemed empty and seemed to refuse to fill. The pulse remained of excessive tension, the rate rising to 148 per minute. The temperature was below 96°. The blood, taken early in the venesection and exposed to oxygen, gave a *saturation of 48 per cent.*; eventually by deep dissection 18 ounces were drawn. The patient was semi-conscious within half an hour of the commencement of the attack, but soon began to recover. After two hours he was much more comfortable and put to bed. The pulse-rate fell to 88 within a few hours of the onset; and the respirations, which at admission were 44 per minute, fell to 24 by the same time, and distress vanished, the colour meanwhile improving conspicuously.

(9. 6. 14.) Next morning he was perfectly comfortable, having slept during the night, and the bronchitic signs having disappeared from the chest, leaving a few crackles at the bases. He was then in much the same condition as at his admission to the Out-patient Department.

(10. 6. 14.) A radiogram showed an aneurysm of the aortic arch. He lay flat in bed without distress and with slight respiratory reserve. The respirations were 28, the pulse 76 per minute. He had very slight cyanosis of the lips. The blood exposed to 17 per cent. oxygen pressure showed *saturation of 60 per cent. in each of two determinations*. The nervous system was found to be normal. The urine contained a cloud of albumin and was of acid reaction, sp. gr. 1,020. A blood-pressure reading taken by Dr. Owen before he was sent was 220 mm. Hg. Immediately after the venesection it was 100, but rapidly rose during the next few days to 180, and oscillated in this neighbourhood. The Wassermann reaction was negative. The temperature rose to normal as the attack subsided and remained so.

(15. 6. 14.) His condition was one of comfort. There had been no further incidents since his attack. The quantity of urine varied between 500 and 2,500 c.c. per diem, being usually as much as 1,500 or 1,600 c.c. The respirations at the time the first blood sample was taken were 20 per minute. The blood exposed to 17 mm. oxygen pressure gave an *oxygen saturation of 65 per cent.*

The paroxysm of breathlessness, which the report covers, and which almost killed the patient, may have been due chiefly, if not entirely, to sudden flooding of the system with acid products. Such being the case in this patient, we consider it highly desirable that attention should be directed to all forms of paroxysmal dyspnoea, from the standpoint of blood reaction during the attacks. It seems possible, if not probable, that many instances of spasmodic dyspnoea may result from a similar causation.

Degree of Acidosis in Cases 1-18.

Case.	Initials.	Date.	Percentage Saturation at 17 mm.	Acidosis in Equivalents of Lactic Acid %.
1	A. A.	8. 11. 13	66, 67	0.01
		28. 11. 13	66	0.01
2	J. L.	16. 6. 13	61	0.02
3	Mrs. G.	26. 11. 13	64-67	0.01
4	Mrs. F.	3. 12. 13	55, 56	0.03
5	T. E.	1. 10. 13	60	0.02
6	G. G.	18. 11. 13	46, 52	0.04
7	G. W.	2. 11. 13	77	0.00
8	Mrs. S.	30. 6. 13	74	0.00
9	Mrs. A.	2. 11. 13	77	0.00
10	M. B.	8. 6. 14	45 circa	0.05 circa
		15. 6. 14	53, 57	0.03
11	J. N.	24. 10. 13	43.5, 44	0.05
12	F. P.	29. 4. 14	75	0
		4. 5. 14	52, 60	0.03
		18. 5. 14	77, 79	0
13	A. L.	15. 12. 13	52, 56	0.03
14	T. D.	24. 12. 13	59, 60	0.02
		30. 12. 13	67	0.01
		26. 1. 14	70, 72	0.00 +
15	M. G.	2. 6. 14	34	0.07
16	Mrs. W.	3. 12. 13	49, 53	0.04
		10. 12. 13	66	0.01
17	W. H.	30. 12. 13	54	0.03
18	J. B.	8. 6. 14	48	0.04
		10. 6. 14	60, 60	0.02
		15. 6. 14	65	0.01

REFERENCES

1. Lewis, Ryffel, Wolf, Cotton, and Barcroft, *Heart*, Lond., 1913-14, v. 45.
2. Lewis, *Brit. Med. Journ.*, 1913, 2. 1417.
3. Poulton and Ryffel, *Journ. of Physiol.*, Camb., 1913, xlv. Proc. 47.
4. Straub and Schlager, *Munch. med. Wochenschr.*, 1912, lix. i. 569.
5. Barcroft, J., *The Respiratory Function of the Blood*, 8vo, Cambridge, 1914.

OBSERVATIONS ON THOMSEN'S DISEASE

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With Plates 8-12

ALTHOUGH many observers have written on Thomsen's disease, the condition still remains almost as much a mystery as when Thomsen first drew attention to it in 1876. He described the disorder as manifested in himself and other members of his own family. 'In answer to a voluntary nervous impulse, difficulty is experienced in the muscles. There develops a tonic cramp condition in the biceps, for example, which then becomes stony-hard and only slowly recovers.

He concluded that the basis of the disease was psychic, arguing from the fact that mental excitement caused augmentation of the symptoms.

Other writers, impressed by the abnormal histological appearance of the muscle fibres, have described it as a primary muscular condition.

Of the earlier accounts, the most complete is that given by Hale White in the Guy's Hospital Reports for 1889. Having weighed the evidence as put forward to that date, he inclined to the view that the disease was primarily muscular. The histological evidence, which he confirmed, showed that a marked difference existed between the appearance of the muscle fibres in Thomsen's disease, and those obtained from a normal subject in the post-mortem room. In Thomsen's disease, it was stated, the voluntary muscles showed fibres of considerably greater breadth than normal. Transverse striation was less well marked and the nuclei in the sarcolemma were more numerous than in the normal.

Opponents of the muscular theory pointed out that these changes might wholly or in part be due to the fact that in the one case muscle was obtained fresh from the living subject and in the other from the dead, and that therefore the comparison was not above criticism. Hitherto, as far as we can find, the histology has not been worked out against a normal living control.

Since 1889 much has been contributed to the literature of the disease by other writers. In this Journal for 1912 are two separate accounts, one by Wardrop Griffith and the other by Findlay. The former brings forward the important observation that the same muscle, which gives a typical myotonic contraction on voluntary effort, responds normally when brought into activity

by reflex action. And finally, in his review of all the evidence, Griffith states that in his opinion 'Myotonia is not altogether due to alteration in the structure of the muscle'.

Both these observers noted the response to electrical stimuli and found that to mild currents of either faradism or galvanism reaction was in every way normal, while with strong currents relaxation was prolonged. Findlay states that with the same strength of current a normal response is obtained with a momentary stimulus and a myotonic one with a prolonged stimulus.

Our own observations have been made on three examples of the disease, members of the same family, who have been under the care of Dr. Hertz, in the Neurological Out-patient Department at Guy's Hospital. To him we are indebted for the opportunity of making this investigation.

The family history is as follows: There were eight children in all, four of whom were apparently normal. Of the other four, three are the patients we have investigated (A. T., male, 24 years; E. T., female, 18 years; and A. H. T., male, 13 years); and the fourth, who was drowned at the age of 17 years, was a twin brother of the girl E. T. The relatives state that he was conspicuously slow in movement, but in spite of this he was able to follow the occupation of a sailor; it is possible that his death was to some extent the result of his myotonic condition. In passing, it is of interest to point out that in the case of the twins both children were affected. The following list of the family, arranged according to age, shows the sequence of the disease in the various members:

- (1) Male, A. T., 24 years. Myotonic.
- (2) Male, H. T., 20 years. Normal, serving in the army in India.
- (3) Male, S. T., 19 years. Normal, serving as second mate at sea.
- (4) Female, E. T., 18 years.
- (5) Male, A. R. T., drowned at the age of 17 years. } Twins, both myotonic.
- (6) Female, W. T., 15 years. Normal.
- (7) Male, A. H. T., 13 years. Myotonic.
- (8) Female, 10 years. Normal.

All three of our patients complained of the same general trouble, namely, that muscular movements had been slow and accompanied by a certain feeling of stiffness ever since they could remember. This was chiefly noticeable in the leg and hand movements. The trouble was worse when the patient was called upon to make any sudden exertion. Thus E. T., who was a maid-servant, stated that if she rose suddenly from her chair to answer the bell, she would remain rooted to the spot for several seconds before being able to make a step forward, and that at school she had never been able to drill like other children. Similarly, A. T., who is now doing attendant work in an infirmary, is so slow with his movements that he is regarded as being purposely slothful and lazy. The youngest patient, A. H. T., first attracted attention to himself by his inability to go up and down stairs as quickly as his younger sister. Our patients in every instance are agreed that their condition has become progressively worse—chiefly from the point of view of increasing muscular weakness—an observation which differs somewhat from the experience of other writers.

The general appearance of our patients was very similar. The face, rather devoid of expression, approximates to the myopathic type. Muscular development is everywhere very pronounced, and this feature was so striking in the case of the boy A. H. T. that his appearance was that of an infant Hercules. Indeed his condition led, at one time, to the suggestion of a diagnosis of

pseudo-hypertrophic muscular dystrophy. The photographs (Figs. 1 to 6, Plates 8 and 9) illustrate these points.¹

On carrying out a systematic examination of the muscles certain facts concerning the myotonic condition were brought out.

In the first place, although the muscles are enlarged they are weaker than normal, as will be seen below. It may be stated here, however, that all muscles are not enlarged to the same degree in the different patients. For example in one case, A. T., the masseters were exceptionally bulky, while in another, A. H. T., the mylohyoids were of such a size as to result in the production of a double chin.

Secondly, in the same patient, certain muscles showed the myotonic contraction more markedly than others. Thus, A. T. after firmly closing the hand was able to relax it completely in 4.8 sec., whereas if the eyes were firmly closed 21 sec. elapsed before complete relaxation occurred. See Figs. 7 (A. H. T.) and 8, Plate 9.

Thirdly, in different patients the muscles chiefly affected with myotonia were not the same. We have no suggestion to offer as to why this variation existed, unless perhaps it was determined by the difference in the occupational pursuits of the individuals. For instance, E. T., whose work consisted mainly in scrubbing and polishing, had the chief trouble in the hands, and A. T., who spent most of his time doing messages and tidying up generally, was mainly troubled with his legs. In another case this explanation would seem scarcely to suffice as the patient experienced much stiffness in his jaws when eating, a symptom not very marked in the other two cases.

Fourthly, the length of time for which the myotonic contraction persisted was influenced directly by the amount of energy put into the movement by the patient. This could be well shown in the case of the orbicularis palpebrarum. If the patient closed his eyes in the ordinary way, without undue effort, relaxation could be accomplished in 10 to 12 sec., while after 'screwing them up' the time occupied was 21 sec.

We have confirmed in our cases the interesting and important observation recorded by Wardrop Griffith that the same muscle which gives a myotonic response when contracted by voluntary effort, gives a normal one in reflex actions. As he states, the latissimus dorsi serves to illustrate this. If the muscle be watched during an attack of coughing (reflex activity), a normal short contraction is observed, while a myotonic contraction ensues in the muscle if the arm is voluntarily brought down to the side against resistance.

The theory of the opposing muscles. The suggestion that the delay in relaxation may be due to the weakness of the opposing muscles need hardly detain us. The fact that after repeated contractions the condition, instead of becoming augmented, tends to wear off is sufficient to negative this. Further, we have tried the effect of continued stretching of the forearm extensors by passively holding the fingers in a flexed position for some time. We found that this produced no alteration in the subsequent series of myotonic contractions. Similarly, if the eyes are passively closed with the fingers, the patient is able to open them without any delay.

¹ The Editor of the *Proc. Roy. Soc. Med.* has kindly given permission for the republication of these clinical illustrations. See *Proceedings*, vii, No. 8, June, 1914.

The Effect of Mechanical Stimulation.

(1) *Of nerves.* The result of rolling the ulnar nerve firmly beneath the finger showed no difference from what occurred in normal persons. The nerves in Thomsen's disease, as observed in our cases, therefore, show neither increased nor decreased irritability.

(2) *Of muscles.* If the surface of a muscle is heavily percussed with the finger a groove at once appears and lasts for a considerable time, due to the local contraction of the muscle bundles directly stimulated. [This is not a characteristic of Thomsen's disease; it is met with to a slight degree in the normal person and particularly in any very muscular individual—such as a gymnast.] The phenomenon was well seen in our patients in the biceps, deltoid, scapular, pectoral, and forearm muscles. The length of time which the contraction lasted varied from 6 to 10 sec. The factor which determined this variation in the length of the contraction we found to be the degree of force with which the muscle was struck. A short contraction invariably followed a light percussion, while the maximum was obtained when the muscle was sharply struck. Fig. 9, Plate 9, shows the grooves produced in this manner in the deltoid. On the other hand, when the tone in the deltoid was reduced by supporting the arm at right angles, the muscle then being quite flaccid, mechanical stimulation evoked no contraction.

Other Clinical Points.

Careful examination of the nervous system revealed no abnormal physical signs in any of our patients. The superficial and deep reflexes were normal. Sensation was unaffected, and special tests for co-ordination, muscle and joint sense also gave evidence of no abnormality. In addition, there was no loss of stereognostic sense.

In the case of A. T. a noticeable feature was the marked condition of dyspnoea which occurred after any period of activity. Thus after ascending one flight of stairs, his respirations were greatly increased and his blood pressure rose 13 mm. of mercury (101 mm. to 114 mm.). The blood pressure of the normal control (W. J.) was raised only 1 mm. (99 mm. to 100 mm.). After the patient had ascended four flights of stairs, there was real respiratory distress which lasted some ten minutes. These facts suggested the question as to whether the respiratory and the cardiac muscle were affected. The heart did not appear to be enlarged when examined either by percussion or by X-rays. An electro-cardiogram taken from the patient by Dr. G. H. Hunt was in all respects normal. It would seem, therefore, that it is the respiratory muscles which are chiefly to blame, a statement which is supported by the behaviour of the patient under the anaesthetic, recorded below. Dr. Hertz, however, informs us that he has examined the diaphragm in all cases under the X-rays and he was able to find 'no evidence of myotonus of the diaphragm either during ordinary or deep respiration'.

Permission was obtained from the patient A. T. for the removal of a portion of the biceps muscle of his left arm for histological purposes. He also agreed to have the median nerve stimulated under an anaesthetic.

He was anaesthetized by means of ether. The necessary operative procedure was very kindly performed by Mr. E. C. Hughes. An incision was made exposing the inner edge of the biceps muscle of his left arm. The median nerve was exposed and stimulated electrically by means of a copper electrode, with results noted hereafter. A strip of muscle, measuring $\frac{1}{2}$ " \times 1", was then excised from the belly of the biceps.

We would here draw attention to the patient's condition under the anaesthetic and after. Open ether was carefully administered. The early stages were made difficult by the general muscular spasm. Respiration was irregular and cyanosis persisted throughout. Instead of the usual recovery within a few hours, the patient remained in a semi-stuporous condition until late in the following day. There was marked pallor, respiration was shallow and the pulse slow; and this despite the fact that examination of the heart and lungs and of the urine had shown nothing abnormal. His state gave rise to considerable anxiety. It is therefore apparent that the administration of anaesthetics in Thomsen's disease is not devoid of grave risk.

One of the writers was next anaesthetized with nitrous oxide and a corresponding strip of muscle removed from the left biceps muscle.

Histological Investigation.

As we have previously remarked, the muscle in Thomsen's disease has never before been compared with muscle removed under similar conditions from a normal living person. In the account which follows, the small portion of muscle removed from our patient, A. T., was compared with the muscle of one of ourselves (G. M.). Our results therefore are not subject to the fallacies present in previous observations and are, in our opinion, conclusive.

As far as possible we have taken into consideration and minimized all those factors which are known to produce variation in the size of muscle fibres. In the first place, the age and sex of the individuals were the same. Then, as the size of fibres varies with individual muscles, the portions to be examined were taken from the same muscle (the biceps) and from the same arm (the left). These portions were then treated in exactly the same way. One part was teased fresh in glycerin, another was fixed in Zenker's fluid, and another in 10 per cent. formalin. There still remains one other factor to be considered, which might be advanced against our results. It is that in a very muscular person the muscle fibres tend to have a larger diameter than in the ordinary individual. In the clinical account of our cases, reference has already been made to the degree of hypertrophy of all the muscles of the patient. Accordingly his biceps was somewhat larger than the control, but as this difference was not in any way extreme, it cannot be regarded as accounting for the marked contrast in the two muscles which will be described below.

One description will serve for all the specimens prepared in the various ways mentioned above. The microscopical appearances were identical in all of them, with the exception that the portion fixed in Zenker's fluid showed the striations rather better than did the others.

The muscle removed from the patient shows a marked increase in the size of the fibres. The interstitial tissue is normal in amount and in appearance. Fresh tissue stained with osmic acid shows a complete absence of fat, both in the interstitial tissue and in the muscle fibre. The increase is entirely due to an excess of sarcoplasm. By actual measurement, the individual fibres in the normal control worked out to 0.07 mm., and those in Thomsen's disease to 0.145 mm., rather more than twice the normal. See Figs. 10 and 11, Plate 10, and compare with the normal 12 and 13, Plate 11.

The other outstanding feature in the transverse sections is the great increase in the number of nuclei. For the main part these lie in the normal position just beneath the sarcolemma, and again are almost double the number seen in the normal fibres, viz. average number per fibre is 7.5, while that of the normal is 3.8. In addition, several nuclei are to be found in the substance of the sarcoplasm—a reversion to the condition which exists in the voluntary muscles of certain animals below mammals. The size of the nuclei do not appear to differ in the two specimens.

As regards the sarcolemma itself, it is perfectly homogeneous and of normal thickness. The sarcoplasm possesses the same staining properties as the control, and in appearance is exactly similar to it.

Under the highest magnification further points could be made out. The longitudinal and transverse striations are equal in size and character to normal. See Fig. 14, Plate 12, and compare with that of the normal 15. We cannot confirm the differences which other writers describe. In sections stained with phospho-tungstic haematoxylin, the individual fibrils are clearly demonstrated. They differ in no way from the fibrils in the control and exhibit the same tendency to break up into still finer strands—the so-called ultimate fibrils. We would therefore conclude that the muscle in Thomsen's disease owes its increase in size to the presence of a larger number of fibrils in each muscle fibre and not to an increase in size of the individual fibrils.

The Red Muscle Theory.

We see, therefore, that histologically the muscles in a case of Thomsen's disease show marked and definite deviations from the normal. The question arises, Is this altered structure of the muscular tissue the primary factor in the disease?

Knoblauch has suggested that Thomsen's disease is due to the muscles containing an abnormally high proportion of 'red fibres'. It is well known that in the rabbit, for example, some muscles are red and some pale. The red fibres are less easily stimulated, contraction is less powerful, and relaxation much

slower. Histologically, the red fibres show nuclei scattered in the sarcoplasm as well as under the sarcolemma. Transverse striation is less regular. Opinions differ as to whether the individual fibres are narrower or broader than the pale variety.

In so far as we have demonstrated the presence of nuclei in the substance of the sarcoplasm in our cases of Thomsen's disease, this theory gains some histological support.

Noyans and Uexküll made a careful study of the respective properties of red and pale muscle in the lower animals. They showed that the red fibres take little part in producing sudden movement of a limb; but the new position having been taken up, the red fibres maintain the muscles in their shortened condition with a minimal expenditure of energy.

If the enlarged muscles of our patients contained an abnormally high proportion of these tonic red fibres, we should expect that although there might be a decrease in the power of quick voluntary movement, yet there would be considerable increase in the length of time which that contraction could be maintained.

This was tested by two simple experiments. A weight was suspended over a pulley by means of a cord. The cord ended in a loop which was attached to the patient's index-finger. The hand having been secured, the patient was instructed to keep the finger flexed for as long as possible against the pull of the weight.

In the second experiment the patient was simply told to hold the right arm out horizontally from the shoulder until overcome by fatigue. We give the results we obtained from the patient A. H. T., who was compared with a normal boy one year younger and of much less muscular development. Their actual strength of grip was also registered by means of the dynamometer.

	A. H. T.	Normal.
Traction with finger against weight over a pulley	35 seconds	80 seconds
Arm held out horizontally	90 "	180 "
Dynamometer. Right hand	70 divisions	80 divisions
Left "	70 "	92 "

Similar results were obtained on applying these tests to E. T. and a control of the same age and sex.

The enlarged muscles of the myotonic subject therefore show no increase of power in sustaining a prolonged contraction. On the contrary, they are considerably weaker than normal. This deficiency is relatively greater than the loss of muscle power as tested by the dynamometer.

These facts we take to be strong evidence against what may be termed the 'red muscle theory' of Thomsen's disease.

Further Investigations.

We will now proceed to describe the other investigations which we have made in the attempt to determine what portion of the neuro-muscular chain is affected in Thomsen's disease.

With regard to mentality and cerebation our patients were by no means below the average. Reaction times fell within normal limits. For example, to visual stimuli the patient E. T. gave a reaction time of 17/100 sec. A normal control (G. M.) was 16/100 sec.

We were not able to show that mental excitement would cause any augmentation of the symptoms.

Herewith are reproduced a series of myographic tracings which show the character of the muscular contractions in our experiments. These were obtained in the following manner: A flexible india-rubber ball was connected with a recording tambour which marked on a moving smoked surface. The time-marker registered seconds. The subject of the experiment grasped the india-rubber ball in the hand so that contraction of the forearm flexors produced an ascending line on the tracing.



FIG. 16. First series of five contractions by normal control (G. M.). Second series by the patient E. T. taken at 10.30 a.m.



FIG. 17. E. T. Taken at 5.30 p.m.

Fig. 16 shows a tracing of a series of five contractions taken as rapidly as the patient E. T. could perform them. The time taken for the five contractions is 4.0 sec. It is seen that relaxation is incomplete until after the third contraction. The normal control using the same apparatus performs five contractions in 1.4 sec., relaxation being complete after each contraction. These tracings were taken at 10.30 a.m.

Fig. 17 was taken at 5.30 p.m. on the same day as Fig. 16. The patient had been up and about throughout the interval. There is little difference between the morning and evening conditions, but the time for five contractions in this instance is 4.2 sec. as against 4.0 sec. in the morning.

Fig. 18 is a tracing of a series of five contractions taken at 10.30 a.m. from the right hand, after the whole right upper extremity had been immobilized by means of a bandage during the previous twelve hours. Five contractions occupied 6 sec. The arm was then left unbound and was used freely throughout



FIG. 18. A. Normal. B. Patient E. T. after immobilization of arm for twelve hours.

the day, another record, not reproduced, being taken at 5.30 p.m., and this showed five contractions in 4.5 sec.

The result of imposing complete rest, therefore, is to exaggerate the myotonic condition.

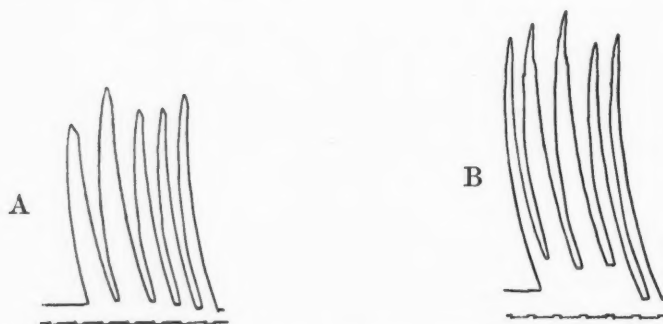


FIG. 19. A. E. T. Left hand. B. E. T. Left hand. Reinforcement by strong grip with right hand.

The effect of what may be termed reinforcement is seen in Fig. 19. While these contractions were being recorded the patient concentrated her attention on another voluntary movement. The time relations were as follows :

	Ordinary contraction of left hand without reinforcement.	Contractions of left hand, during reinforcement by simultaneous sustained contraction of the right.
Total for five contractions	5 seconds	4.75 seconds
1st contraction	1.2 "	0.5 "
2nd "	1.3 "	1.3 "
3rd "	0.9 "	1.2 "

The effect of reinforcement by previous passive hyperextension of the muscle tested is seen in Fig. 20:

	Before hyperextension.	After hyperextension.
Total for four contractions	3.4 seconds	3.2 seconds
1st contraction	0.8 "	0.6 "
2nd "	0.9 "	0.5 "
3rd "	0.6 "	0.8 "



FIG. 20. A. E. T. Right hand. B. E. T. Right hand after previous passive hyperextension.

Reinforcement it appears, therefore, causes a quickening up of the first contraction with a subsequent swing back and slowing of the later ones. This is similar to the reaction produced in normal individuals.

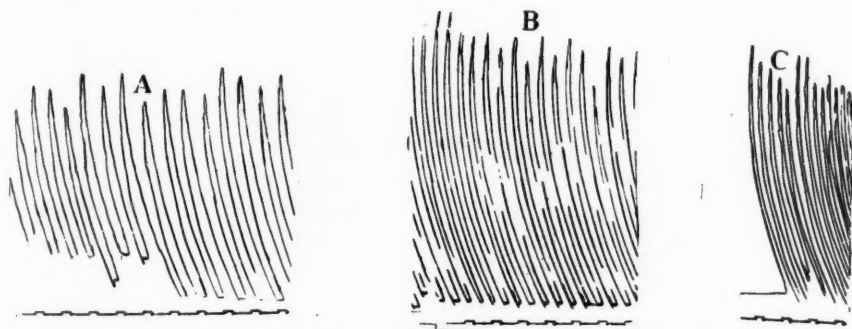


FIG. 21. A. Part of a long series of contractions by E. T. B. Another strip from same series later. C. Normal control (W. J.).

A long series of contractions, performed as rapidly as the patient E. T. was able, is seen in Fig. 21. It is seen that after a time the myotonia tends to wear off, but the rate is still nearly twice as slow as that of the normal control.

The patient's best is ten contractions in 5.0 sec. The normal is ten contractions in 2.9 sec.

The effect of alterations of the local conditions of the muscles tested is seen in Fig. 22:

A. Forearm exposed to air at temperature of the ward, 15.1 C. Five contractions in 6 sec.

B. After immersion of forearm in water at 43° C. for 15 min. Five contractions in 6 sec.

C. The forearm having been rendered ischaemic by application of a tight bandage from below upwards. Five contractions in 7.3 sec.

D. The forearm was rendered congested by the application of a tourniquet to the upper arm, without the obliteration of the radial pulse.

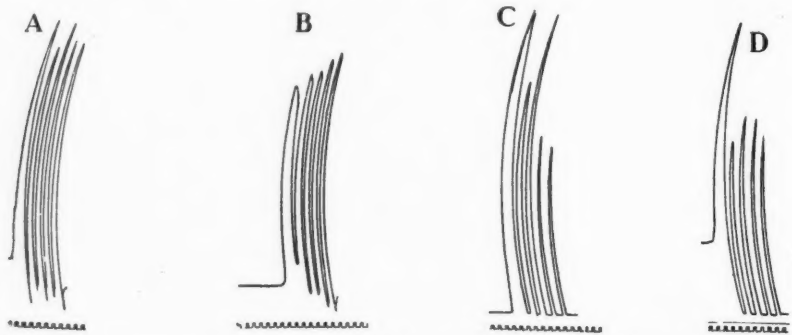


FIG. 22. A. Forearm exposed to air at 15.1° C. B. Forearm immersed in water at 43° C. C. Forearm ischaemic. D. Forearm congested.

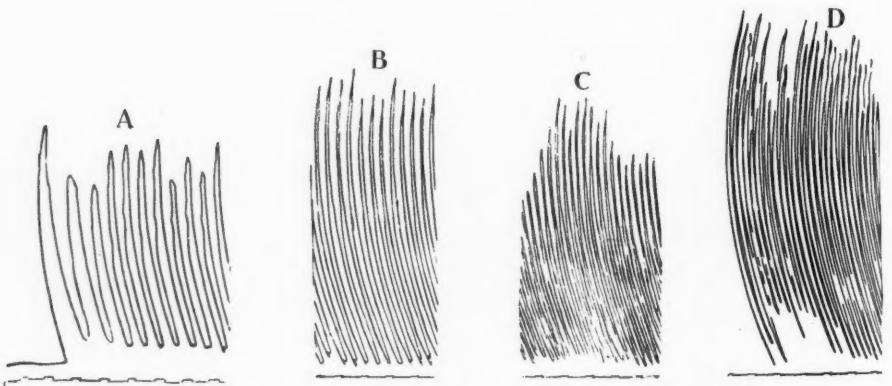


FIG. 23. A, B, and C are successive strips from a long series of contractions by the patient E. T. after two hypodermic injections of strychnine. D. Normal control (W. J.).

Fig. 23 demonstrates the action of strychnine. Two hypodermic injections of the liq. strychninae, five minims on each occasion, were given at an interval of four hours. The tracing was taken half an hour after the second injection. The first five contractions were completed in 4.5 sec., which is slightly quicker than the patient's average. It is of great interest to record, however, that after repeated contractions the myotonic condition disappeared, a series of five con-

tractions being completed in 1.4 sec. If this be compared with the controls, it is seen to be within normal limits, the normal person giving readings for five contractions varying from 1.25 to 1.45 sec.

Electrical reactions. Stimulation by means of electrodes placed on the skin over the motor points gave results similar to those obtained by other observers, to which we have already referred. Momentary stimulation with weak faradic currents gave rise to brisk contractions followed by prompt relaxation. Strong currents produced a spasm of the muscles followed by a condition of prolonged relaxation.



FIG. 24. Faradism, repeated momentary stimuli.

Fig. 24 is a record of a series of contractions in answer to quickly repeated momentary stimulation with a weak faradic current. The rate of contraction by this means rose to that of five in 1.8 sec., which it will be noticed is quicker than the patient was ever able to accomplish by her own voluntary effort. A reference to Fig. 21 will show that this was five in 2.6 sec. A further reference to Fig. 23 will show, however, that the rate was still below that which resulted after the administration of strychnine. There still remains to be recorded the results obtained by direct stimulation of the median nerve, under the anaesthetic. At the moment of stimulation the corneal reflexes were abolished, and the muscles were in a state of relaxation. One electrode was applied to the palm of the hand, the other to the median nerve exposed in the incision half-way down the upper arm. Momentary stimulation was given with a weak faradic current. This was followed by a prolonged contraction of the forearm flexors; relaxation was slow, not being complete until 15 sec. after the moment of stimulation. After a short interval this procedure was repeated, but, instead of a momentary stimulus, the faradism was given continuously for five seconds. A powerful contraction again ensued, but, on this occasion, relaxation was complete eight seconds after the shutting off of the current. In this experiment, therefore, it is shown that a prolonged stimulus did not produce a longer relaxation period than did a momentary stimulus.

Summary of Results.

Of a family of eight children, four were found to be affected with Thomsen's disease. It has been possible to investigate three of these carefully. We found the physical signs of the nervous system were normal; that the muscles in all three cases were larger than normal, but the actual strength of contraction and ability to maintain that contraction for any length of time were below normal.

The myotonic contraction does not occur in reflex action.

The duration of the local contraction produced in a muscle by mechanical stimulation varies with the degree of force used by the percussing finger. In one case, dyspnoea was easily provoked by any exertion, and this patient took an anaesthetic very badly.

Also, in one case, we have carried out a histological investigation of the muscle and compared it with muscle removed from a normal living control. We find that in Thomsen's disease the muscle fibres are larger than normal, their diameter being about twice the normal size. This increase is entirely the result of increase in the number of fibrillae in each fibre. The nuclei are in proportion to the size of the fibres, that is to say, there is no relative increase. Some of the nuclei occupy a position in the substance of the sarcoplasm. The longitudinal and transverse striation of the fibres showed no variation from the normal.

In another case a series of myographic tracings were taken. We find that there is no definite alteration in the contractions whether taken in the morning or in the evening after a day's activity. Complete immobilization of a limb for twelve hours produces exaggeration of the condition in the muscles so rested. After numerous repetitions of a movement, the action becomes more brisk, but our patient was always twice as slow as a normal control. 'Reinforcement' quickened up the first movement of a series at the expense of the later ones, thus conforming to the reaction met with in the normal subject. Alterations in temperature produced no registerable effect. Ischaemia and congestion both caused lengthening of the contraction.

Electrical stimulation by electrodes applied to the skin showed that weak stimuli produced brisk contractions, and strong ones a prolonged spasm. With the patient anaesthetized we were able to stimulate the median nerve directly with weak faradism. Momentary stimuli produced a contraction which persisted for 15 sec. and prolonged stimulation a contraction which lasted only 8 sec.

After two hypodermic injections of strychnine the muscular movements became practically normal. We suggest the use of strychnine in the treatment of this disease.

Discussion.

We have seen that the 'red muscle theory' fails to explain adequately the known facts.

The observation that the same muscle gives normal and myotonic contractions in response to reflex and voluntary stimuli, respectively, makes untenable the view that myotonia is primarily muscular.

On the same grounds, the action of muscle poisons, such as veratrine and sodium phosphate, would appear to be of a different character from the condition we are investigating.

It is possible that there may be at the root of this disorder either some toxin or some derangement of internal secretion, but we have no direct evidence on these points.

We would suggest that in Thomsen's disease there is an increased resistance to the passage of nervous impulses. This resistance would appear to be in the synapses. The action of strychnine in lessening the myotonic character of the contractions points to this conclusion. It is inconceivable that the small amount of strychnine administered could have had any direct action on the muscles. Strychnine is known to act on the synapses of the central nervous system, facilitating the passage of a nervous impulse from one neurone to the next. This partial block which exists in the disease is temporarily removed by the action of strychnine. It is known that gross lesions of the pyramidal tracts, where the cerebellar tracts remain intact, give rise to a condition of increased muscular tone and spastic movements. A partial obstruction in the higher motor path would account for the symptoms met with in Thomsen's disease. Thus the myotonic character of the contractions is most marked when movement is in response to voluntary effort. On repetition, a movement becomes brisker, as block tends to wear off. On the other hand, reflex movements are normal, for here the higher motor paths are not involved. There is increased tone, which, as we have seen, is to be expected. The abnormal response to a powerful electrical stimulus may be due to this permanent condition of increased muscular tone. We cannot exclude the possibility that it may be an effect produced through the higher centres. From this point of view no experiment can be pure which does not involve actual division of the nerve above the point stimulated.

The histological changes in the muscle we would regard as a secondary effect, a form of compensatory hypertrophy. The permanent condition of increased tone and the prolonged spasm which follows a voluntary contraction greatly increase the amount of work which the muscles are called upon to perform.

At a later date we hope to publish further evidence in support of this theory regarding Thomsen's disease.

DESCRIPTION OF FIGURES.

PLATE 8, FIG. 1. A. T. aged 24 years.

FIG. 2. A. T. aged 24 years.

FIG. 3. A. T. aged 24 years.

FIG. 4. A. T. aged 24 years, showing the position of the hand during slow relaxation.

PLATE 9, FIG. 5. A. H. T. aged 13 years.

FIG. 6. A. H. T. aged 13 years.

FIG. 7. A. H. T. aged 13 years; the eyes being opened.

FIG. 8. A. T. aged 24 years; eyes being opened after having been firmly closed.

FIG. 9. E. T. aged 18 years, showing the grooves on the deltoid caused by tapping with the finger.

PLATE 10, FIG. 10. Transverse section of a portion of the biceps muscle in Thomsen's disease. $\times 360$ diameters.

FIG. 11. Longitudinal section of a portion of the biceps muscle in Thomsen's disease. $\times 360$ diameters.

PLATE 11, FIG. 12. Transverse section of normal biceps. $\times 360$ diameters.

FIG. 13. Longitudinal section of normal biceps muscle. $\times 360$ diameters.

PLATE 12, FIG. 14. Muscle in Thomsen's disease, to show the longitudinal and transverse striations. $\times 700$ diameters.

FIG. 15. Normal muscle, $\times 700$, for comparison with Fig. 14.

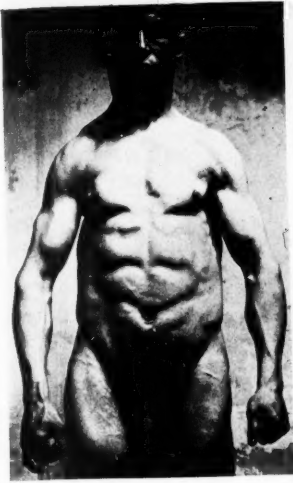


FIG. 1



FIG. 2



FIG. 3



FIG. 4



FIG. 5



FIG. 6



FIG. 7



FIG. 8



FIG. 9



FIG. 10

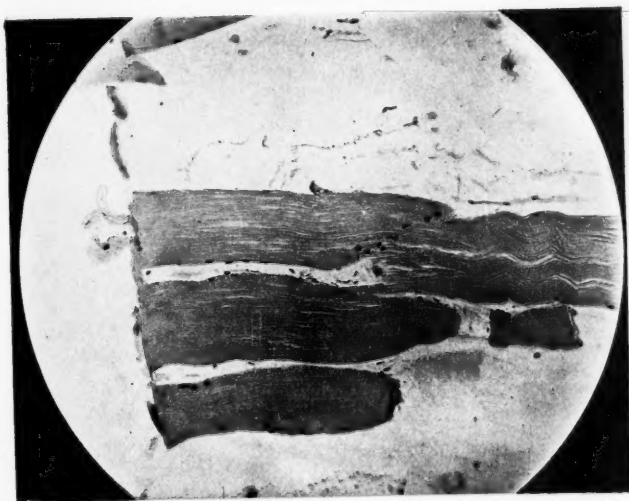


FIG. 11

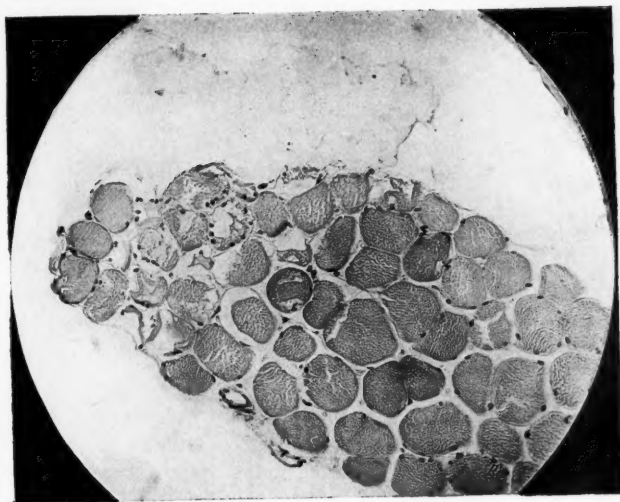


FIG. 12

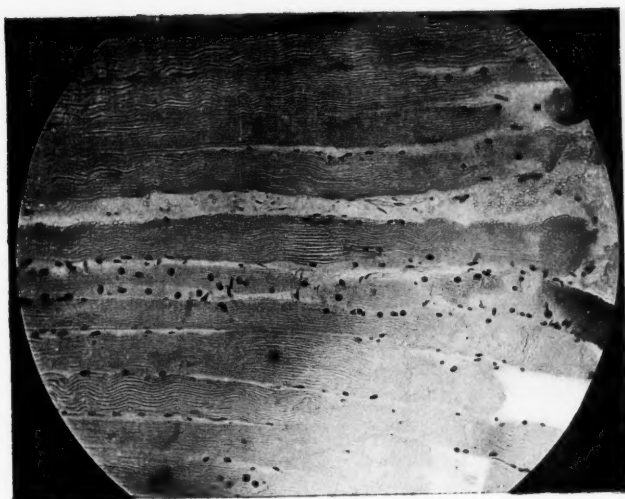


FIG. 13



FIG. 14



FIG. 15

THE RATIONALE OR MODUS OPERANDI OF THE WASSERMANN REACTION AND ABDERHALDEN'S TEST

By J. E. R. McDONAGH

History.

BORDET and Gengou (1) were the first actually to demonstrate the occurrence of an antibody, by means of the complement fixation test. Wassermann did much work on these lines, and, in conjunction with Bruck (2), he published several papers referring to tuberculosis and other diseases from this aspect. Wassermann's next step was to apply this test to syphilis, but he was confronted with the difficulty that the *Spirochaeta pallida* had, up to that time, resisted all attempts to be cultured, and so he was forced to use an extract of a viscus which was rich in these organisms. Consequently, an extract of a foetal syphilitic liver was used as antigen. As such an extract was found to act perfectly well, Wassermann and Bruck (3) brought out their serum diagnosis of syphilis, which has since gone by the name of the Wassermann Reaction.

Owing to the labour entailed in carrying out the complement fixation test, various workers attempted to supplant it by precipitation tests. Fornet and Schereschewsky (4) and Michaelis (5) claimed that they got a definite precipitate, by the action of a syphilitic serum on an extract containing a large amount of syphilitic antigen.

Porges and Meier (6), instead of using a syphilitic antigen, employed a 1 per cent. solution of sodium glycocholate. Klausner (7) merely diluted the sera with distilled water. None of these precipitation tests was ultimately found to give satisfactory results. The next step was Schürmann's (8) colour test. Schürmann was under the impression that syphilitic sera contained lactic acid, and he attempted to demonstrate this with Uffelmann's reagent, and later with perhydrol mixed with phenol and ferric chloride. This test was soon found to be fallacious. Assuming that the modus operandi of the Wassermann reaction depended on a precipitation, Jacobsthal (9) suggested a method which he termed the 'optic serodiagnosis of syphilis'. The patient's serum is mixed with an alcoholic extract of syphilitic liver, and the resulting precipitate is examined by the dark-ground illumination method. A strong positive reaction appears as a clumpy precipitate, and a negative reaction as a thick emulsion of

very fine particles. As Jacobsthal's observation throws some light upon the rationale of the Wassermann's reaction, it will be referred to later.

As no tests could be found to supplant the reaction, various attempts were made to simplify the technique. Levaditi and Yamanouchi (10), instead of using immunized rabbit's serum as the amboceptor in the haemolytic system, relied upon the human serum already present, because human serum contains a natural amboceptor to sheep's blood. The natural complement was also used by Hecht (11), and by Fleming (12). Landsteiner, Müller, and Pötzl (13) next found that an efficient antigen could be prepared from tissues which had never harboured a *Spirochaeta pallida*.

As both amboceptor and complement retain their active properties if dried, measured quantities of these were taken up by measured sizes of filter-paper, dried and dissolved in saline, when required. Modifications in the reaction were also made in order to diminish the number of negative results obtained in syphilitic cases. Cholesterol (14, 20) was added to the antigen, and Wechselmann (15) advocated shaking the sera beforehand with barium sulphate, to precipitate what he called 'complementoid bodies'.

Another test which requires mention, as it has some bearing upon the rationale of the reaction, is the meiotagmine¹ reaction suggested by Ascoli (16), used by him as a diagnostic procedure in typhoid fever, and applied by Izar (17) to syphilis. The test is a physico-chemical reaction of immunity, depending on a change in surface tension when an antibody is brought into contact with its own antigen.

The consensus of opinion is that no test for syphilis is so valuable as the Wassermann reaction, and that all modifications of the original technique detract from the reliability of the test. The attempt to sharpen the reaction, by adding cholesterol to the antigen, has met with great approval, although the view that non-specific reactions are obtained is fast gaining ground. Wechselmann's method has not received much attention, but Lange (18) obtained good results in a series of cases in which both methods were simultaneously performed.

As these modifications to sharpen the Wassermann reaction help to explain the rationale of it, a fuller description of them will be found later.

The Modus operandi or Rationale of the Wassermann Reaction.

In the Wassermann reaction we are concerned with four factors: (1) antigen; (2) complement; (3) antibody; (4) haemolytic system.

As the haemolytic system is common to all complement fixation tests, it is necessary, at present, to discuss the first three factors only. Moreover, the explanation to be given of the modus operandi of these three factors will also clear up the rationale of the haemolytic system, because in both we are dealing with an antigen, complement, and an antibody. Since the antigen need not

¹ *μείων* (smaller), *στράζω* (I drop).

necessarily be an extract of syphilitic material, the reaction ceases to fall in line with the bacterial complement fixation tests originated by Bordet and Gengou (1).

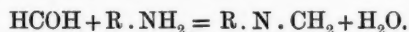
Owing also to the fact that a positive Wassermann reaction may be obtained in conditions other than syphilis, the reaction ceases to be a specific reaction. Therefore, the third factor ought not to be called an antibody, since it is in no wise specific; hence it is best called reacting substance, or reagin, for short.

Antigen.

It is now a well-known fact that one, if not the main, principle in the antigen is a lipid, and that the lipid which has the best action is that in which the ratio between nitrogen and phosphorus is as $N_1:P_1$ (lecithin), as demonstrated by Thiele and Embleton (19). Although we know that the antigen is a lipid, this knowledge is of no great service, as the term 'lipoid' embraces so many substances, some of which have no antigenic properties, and all of which are extremely complex. Therefore, there must be, in the lipid, some active substance, or combination of substances, primarily responsible for the antigenic action. For a substance to have antigenic properties, it appears to be necessary for it to contain nitrogen in its molecule. The nitrogen, in the form of an amino acid, appears to be the active part of the lipid, since artificial antigens can be prepared, provided they contain amino-acid groups. Tested by Van Slyke's method with nitrous acid, but without previous precipitation with alcohol, the antigen which I have always used (extract of congenital syphilitic liver) gave the following amino-acid value:—

Vol. of antigen diluted 1 in 10 with saline.	Vol. of N collected.	Vol. of N from solution.	Vol. of N from 100 c.c.	Weight of N from 100 c.c.
c.c. 5	c.c. 1.00	c.c. 0.50	c.c. 10.00	mg. 11.70
Temperature				85° C.
Pressure of gas				750 m.m.
Weight of one c.c. of N at 15° C. and 750 m.m.				= 1.17 mg.

If a trace of formalin be added to an antigen, the antigenic properties are increased, and, at the same time, the amino-acid content is decreased by about half. Formalin increases the antigen action, because the replacement of the amino groups by a methane group increases the size of the colloidal particle.



The proof that the colloidal particle is increased in size is shown by the fact that the $\text{R} \cdot \text{N} \cdot \text{CH}_2$ molecule requires about three times as much ammonium sulphate to precipitate it as the $\text{R} \cdot \text{NH}_2$ molecule.

Therefore, although an amino group is primarily responsible for the action

of antigen, it is not wholly responsible, since the formalized product will act as an antigen, which leads me to the conclusion that the size of the colloidal particle plays an important part in the reaction.

Three c.c. of antigen were taken and divided into three parts; to 1 c.c. one drop of a 40 per cent. solution of formalin was added (antigen B), and to another 1 c.c. one drop of a 1 in 10 of a 40 per cent. solution of formalin was added (antigen C), antigen A being the control.

Antigen.	Antigen + Complement.	Antigen + Complement + Syphilitic serum.	Antigen + Complement + Normal serum.
A. 1 in 5	—	+++	+
A. 1 in 10	—	+++	—
A. 1 in 20	—	+++	—
B. 1 in 5	+++	+++	+++
B. 1 in 10	++	+++	+++
B. 1 in 20	—	+++	++
C. 1 in 5	—	+++	++
C. 1 in 10	—	+++	—
C. 1 in 20	—	+++	—

A few days were allowed to elapse before the experiment was carried out, so as to be quite sure that no free formalin was present which might fix complement. These same antigens, tested one week and two weeks later, gave approximately the same results. It must be stated that the antigen is neither specific nor absolutely necessary for the Wassermann reaction.

As the Wassermann reaction is generally done, for the fixation to be complete the tube must contain antigen, complement, and a serum containing reagin; but it occasionally happens that reagin and complement alone are sufficient to produce fixation, and to such a phenomenon the term amphoterism or 'Eigenhemmung' is given.

Amphoterism is practically always syphilitic sera. They are more commonly met with in late than in early cases of syphilis, and occur not infrequently in the cases of lymphocytomata of syphilitic origin, although the patient may no longer be in an active syphilitic condition. The amphoterism is due to an excess of lipid which is attached to the globulin molecule. The more lipid there is attached to the globulin molecule, the larger is the molecule, and the greater its adsorptive capacity. Therefore, from the few remarks already made, it looks as if the Wassermann reaction were not a specific reaction, but merely an adsorption or precipitation reaction, depending partly upon the size of the lipid-globulin (reagin) molecule.

Although, in my opinion, an extract of foetal syphilitic tissue gives the best results, there is not very much to choose between this and an alcoholic extract of ordinary, or better, autolyzed material. An extract of spirochaetae acts very indifferently as an antigen, owing to the fact that the emulsion contains sufficient free fatty acid or, what is more probable, that the parasitic lipid-globulin molecule contains an unsaturated fatty acid group, and that this prevents adsorption. When it became generally known that the antigen's active principle was a lipid, several observers manufactured artificial antigens,

and the chief substance added was cholesterol (14, 20, 21), although none of these observers appeared to have any reason for adding this substance. At the present time, great differences of opinion prevail as to whether the addition of cholesterol does not, in sharpening the reaction, by reason of its great adsorptive powers, cause positive results to be obtained with sera which should have given negative reactions. At first, cholesterol antigens found great favour, but several observers in Germany, France, and Italy (25) have recently given them up, owing to the fact that normal sera were found to give positive results.

In England, Thiele and Embleton (19) have come to the conclusion that the addition of cholesterol gives non-specific reactions, and in my research work on the rationale of the Wassermann reaction, I have carried out several experiments with cholesterol about which a few remarks may be stated here.

Provided that the patient's serum is inactivated within forty-eight hours of its withdrawal, and that the serum is neither kept longer than twenty-four hours in an ice incubator, nor longer than ten days at room temperature—and here the time of year plays a rôle—the risk of obtaining a positive reaction in a non-syphilitic case is remote but possible, when an antigen is used which is made up with an aqueous solution of cholesterol, and which has been properly standardized. If, on the other hand, the precautions mentioned above are not observed—often they cannot be, and usually they are not observed—the risk referred to becomes very great.

If it be necessary to make the reaction sharper, there must be grounds for so doing. For diagnosis, the reaction should be seldom required. Failing diagnosis, its next use is to regulate treatment. Making the reaction sharper means the administration of more treatment, until, in the majority of early cases of syphilis, it is impossible to obtain a negative reaction, even two or three years after the most vigorous treatment has been given, when, clinically, we assume the patient to be cured.

Summing up the points which the addition of cholesterol brought to my notice, it will be seen that temperature has an influence upon the reaction and that a serum is more easily affected if it be from a patient who formerly had syphilis, even if he be now cured of the disease. Consequently, the next series of experiments I undertook was to gauge the influence which temperature had upon sera.

Effect of Temperature.

All sera kept at room temperature sooner or later give a positive reaction; a negative serum from a patient who has had syphilis will tend to become positive earlier than a serum from a normal patient. No rule can be made as to when sera become positive, as no two require the same time. I have found a normal serum to give a positive reaction after it had been kept four days, but this is an exception. If kept longer still, when bacterial action has autolyzed the reagin, even strongly positive syphilitic sera will give negative reactions.

If the sera are diluted with saline and then kept, they do not tend to become more positive, but syphilitic sera may become negative, owing to precipitation of the reagin molecules. For the same reason, neither antigen nor complement will keep when diluted. The protein molecules in diluted sera quickly become deionized, and this results in their precipitation. If kept in an ice incubator, all sera develop reagin at a quicker rate than when kept at room temperature. Inactivating beforehand prevents this, to some degree. I have had two cases in which normal sera developed reagin, after having been in an ice incubator for only twenty-four hours. The action of heat also influences the reaction. Many syphilitic sera when inactivated, i. e. heated for half an hour at 57°C ., become negative, whereas, before being heated, they gave a strong positive reaction. Heating sera for longer than half an hour, and at a higher temperature than 57°C ., causes them to develop reagin.

Freezing-point.

The freezing-point of sera was next tested, as I thought perhaps syphilitic sera might give a different reading to normal sera, but such was not the case. All that one could say was that, generally speaking, the freezing-points of syphilitic sera were slightly lower than those of normal sera; but the differences were too small to allow one to separate a normal from a syphilitic case, and even these small differences showed no regular variation when compared with the degree of positivity of the Wassermann reaction.

The factor upon which the freezing-point of sera is dependent is the concentration of the free salts. The concentration of the free salts begins to vary after the sera have been kept for twenty-four hours; hence no reading is accurate unless it is made before that time.

The freezing-point of normal sera, according to Rona (22), varies from -0.517°C . to -0.562°C . If the sera are kept longer than twenty-four hours, the freezing-point becomes lower, which suggests that the concentration of the free salts increases.

Sera which have been tested for the freezing-point may be used for the Wassermann reaction afterwards, provided they are only frozen once and for as short a time as is practicable. If the first reading be inaccurate, and another be required, i. e. if the serum is frozen twice, the second reading has a tendency to be lower than the first, and such a serum may have developed reagin. Freezing sera for a longer period than is required for ordinarily reading the freezing-point will often make a negative serum give a positive Wassermann reaction.

Active Sera.

Since inactivation may destroy reagin, I have tested over 2,000 sera side by side, active and inactive, with the result that a far greater percentage of positive reactions were obtained in syphilitic sera when they were used active; a few

syphilitic sera reacted positively only when inactivated; and, very occasionally, a normal serum in the active condition gave a positive reaction. (Five cases.)

Theoretically, it might be imagined that if a serum was used active, the additional complement would suffice to give a negative rather than a positive reaction. Practically, that is not the case, the reason being that complement and antibody (reagin) are the same substance chemically, and since complement becomes antibody, no hard and fast line can be drawn between them. Moreover, when complement becomes antibody, it often loses its complementary properties, for frequently syphilitic sera are to be met with in which no complement can be demonstrated. It may occasionally happen that a serum will give a more positive reaction when inactivated than when used active. This is probably due to the fact that free fatty acid molecules exist in the active serum, and that, when the serum is heated, more fatty acid molecules and, in addition, amino-acid molecules are also set free from the reagin particle, and either of them, if in excess, can fix complement.

Inactivation injures the reagin molecule. The action of reagin, as will be later shown, is one of adsorption and consequent precipitation. The adsorptive capacity of a molecule is partly dependent upon its peripheral atoms, or, in other words, ions. Therefore, it will at once be seen that, so far as the pure complement fixation test is concerned, sera should always be used active. The reagin molecule, when in the active condition, is more as it is when in the body, and the so-called complement which is attached to it only increases its anti-complementary action, and vanishes in the process.

Pressure.

The next experiment was to test the effect of pressures both greater and less than that of the atmosphere. For minus pressure, sera were left for forty-eight hours under 500 mm. of Hg instead of 760 mm., at 10° C. For plus pressure, sera were kept for forty-eight hours under 850 mm. of Hg instead of 760 mm., at 10° C. The action of both was the same, so they can be considered together. Normal sera tended to develop reagin, the degree of fixation depending, as was found throughout this work, upon how long the sera had been kept, upon the temperature at which they were kept, and upon whether the antigen contained cholesterol or not. Syphilitic sera which gave a negative or a weak positive reaction become very positive, and those giving a positive reaction become amphoteric.

Neither a minus nor a plus pressure is able to convert an amphoteric serum into a negatively reacting serum. The action of a minus pressure upon sera is probably to increase the size of the colloidal particles by precipitation. The action of a plus pressure upon sera is probably to cause partial hydrolysis, which would result in there being an excess of amino and fatty acid molecules. The lowering of the surface tension is much more marked in those sera which

have been subjected to a minus pressure, a point in favour of precipitation as against hydrolysis.

Wechselmann's Barium Sulphate Modification.

As Wechselmann (15) some years ago had shown that shaking a negatively reacting syphilitic serum with barium sulphate often resulted in the serum becoming positive, I tried a series of experiments with this salt and kaolin, Kieselguhr, silicic acid (Kieselsäure), and iron hydroxide. Barium sulphate is non-colloidal. Kaolin ($H_2O, Al_2O_3, 2 SiO_2$) is only partially colloidal. Kieselguhr is practically SiO_2 and therefore colloidal. Kieselsäure is $Si(OH)_4$ and therefore strongly colloidal, and so is iron hydroxide, which is $Fe(OH)_3$.

The more colloidal the body, the less influence it had in causing an alteration in the reactions, and vice versa. Barium sulphate tends, but slightly only, to make normal sera positive; time, temperature, and cholesterol are, as usual, influencing factors. Syphilitic sera giving a negative reaction become positive; those giving a feeble positive reaction become markedly positive; those giving a positive reaction become amphoteric; while primarily amphoteric sera remain unchanged.

Kaolin has a similar action but to a much less degree. Kieselguhr is feebler still, while Kieselsäure and iron hydroxide are without action. Therefore the degree of activity varies inversely as the colloidal nature of the body added.

Now comes the question as to how barium sulphate acts. Barium sulphate cannot carry down ions, since it is itself non-ionizable. It can take down some fatty acids, but this alone would not suffice to account for the increased positive reaction, which, in some cases, is often considerable. Barium sulphate, being non-colloidal, no doubt increases the size of the protein colloidal particles, and in this way acts as a very slight protein precipitant. The more vigorously the barium sulphate serum is shaken, and the longer the salt is kept in contact with the serum, the more positive will the reaction be, as protein precipitation is increased. Polarimeter readings carried out at different intervals confirm this.

To prove that barium sulphate acted by precipitation, I examined with the stalagmometer a series of sera before and after treatment with barium sulphate. The stalagmometer measures the surface tension. The surface tension of a colloidal solution is maintained by the colloidal particles in the solution, hence it will follow that if the colloidal particles are precipitated, the surface tension must be lowered. The barium sulphate-treated sera were found to have a slightly lower surface tension than the plain sera. Here it may also be stated that plain syphilitic sera cannot be differentiated from plain normal sera by measuring their surface tension.

Ascoli and Izar (16, 17) showed that the surface tension of syphilitic sera was lowered, when antigen and complement were added thereto, but not when

added to normal sera—a fact which proves that the mixture of antigen, reagin, and complement results in a precipitation of certain colloidal particles, and this could not have come about without previous adsorption.

Reagin.

The question now arises as to what reagin is. If my work on the chemistry of the leucocytozoon syphilidis be referred to (23, 32, 34) it will be seen that the phases of the parasite are rich in lecithin-globulin, and that the protoplasm of the plasma cells also contains this substance. It is a well-known fact that the host protects itself with weapons of the same nature as those with which it is attacked. It is, moreover, common knowledge that protective substances, although originating in cells, do not remain intracellular: they circulate in the blood, or, more strictly speaking, in the serum.

Wassermann and Lange (24) recently showed that the reagin substance in the cerebro-spinal fluid came from the cells which constituted the lymphocytosis. This is true so far as it goes, but it is not only from the lymphocytes that the reagin originates; it also comes from the epithelial cells of the choroid plexuses. The epithelial cells of the choroid plexuses and Nissl's granules are made up of lipid-globulin adsorption complexes. If the reagin in the cerebro-spinal fluid comes from these cells, it rather suggests that the reagin is a lipid-globulin. One of the functions of these lipid-globulins in syphilis is, as I have shown elsewhere (29, 30), to carry oxygen ferments. Now the cerebro-spinal fluid in cases of degenerative encephalitis is rich in oxydases: the epithelial cells of the choroid plexuses and Nissl's granules give marked oxydase reactions; therefore the proof is strong that the reagin is the same substance as the lipid-globulin of certain cells.

It becomes still stronger, when attention is called to the fact that the amount of globulin in the cerebro-spinal fluid is increased in cases of syphilitic lesions of the central nervous system, and that this globulin is frequently to be found in an adsorption complex with a lipid.

Thinking it highly feasible, then, that the reagin was lecithin-globulin, I next tried a series of experiments to find out the action of pure lecithin-globulin upon complement, and then added it to sera and repeated the same experiments with butyric, palmitic, stearic, and oleic acids, alone, with normal sera (human and equine), and with lecithin-globulin. Similar experiments were conducted with tripalmitin, tristearin, and triolein, and also with other nitrogen and phosphorus-containing lipoids, namely, cerebrin and protagon. As very similar results were obtained, space may be saved by giving a general statement of them.

The lecithin-globulin used in these experiments was obtained from a case of pseudochyolous ascites and kindly given to me by Dr. Mackenzie Wallis. A saline emulsion of this lecithin-globulin did not deviate complement, and, when added

to normal sera, it produced no change in the reaction. When added to syphilitic sera, in some it made no alteration, in others it either increased or decreased the reaction. Its most usual effect was considerably to decrease the reaction in all stages of syphilis; in fact, an amphoteric serum, under ordinary circumstances, often gave a negative reaction on the addition of lecithin-globulin. In only the minority of instances was a negative reaction converted into a positive one, and the only cases in which this happened were patients in the latent stage of syphilis.

The reason why positive sera became negative was probably because the lecithin-globulin emulsion contained some free fatty acid which, if not too great in amount, can readjust complement, or prevent adsorption. The reason why negative syphilitic sera became positive was probably due to the reagin containing free fatty acid groups, which primarily were responsible for the negative reaction, and these free fatty acid groups, plus those contained in the lecithin-globulin emulsion, were sufficient to fix complement, since excess of fatty acids has this action.

All the fatty acid mixtures had a similar action, although they differed in degree, the action of oleic acid being the most pronounced. Normal sera tended to develop reagin, a phenomenon dependent upon the length of time the fatty acid had been in contact with the serum. Syphilitic sera giving a negative reaction usually became markedly positive. Syphilitic sera giving a feeble positive reaction often became amphoteric. Sera giving a strong positive reaction, and those which were primarily amphoteric, often became completely negative.

The different results depend, as in the previous case, upon the amount of free fatty acid: if in excess, then fixation of complement; if not in excess, then readjustment of complement. The fatty acid esters, or triglycerides, had a strong anticomplementary action, and all sera became positive or amphoteric. Occasionally, most contradictory and irregular results were obtained with the triglycerides, and I found later that these results were due to the powerful action which certain sera had in breaking down the triglycerides into their corresponding fatty acids. Cerebrin, broadly speaking, behaved like a fatty acid, while protagon acted as a triglyceride. Both were easily broken down into free fatty acids.

From the behaviour of the saline emulsion of lecithin-globulin in the preceding experiment, doubts might be cast upon my view that the reagin is of a lecithin-globulin nature.

Lecithin-globulin cannot be extracted from the fluid in which it is, unless it is precipitated; therefore, in the process of precipitation some change may have taken place, which would alter its physical properties. Precipitated globulin will fail to give the Goldsol reaction, because in the process of precipitation the globulin has lost its electric charge—or, in other words, has had its ions detached. The same with the lecithin-globulin. When the lecithin-globulin is added to a normal serum, the reaction becomes positive, which

proves that the natural lipid-globulin in the serum has adsorbed the foreign lecithin-globulin, with the result that its molecule is increased in size and made to resemble reagin.

It is only the lipid-globulin molecule in the serum which is capable of forming adsorption complexes; therefore, it would appear that reagin is lipid-globulin, the molecule of which has reached a certain size, and that it is a molecule which is capable of adsorbing other similar substances owing to the ions which are attached thereto.

Complement.

All we know about complement is, that it quickly vanishes when kept, that it is thermo-labile, that it can be preserved for a period in concentrated salt solutions, that when once destroyed it cannot be rejuvenated, that it can be destroyed by shaking and by continued centrifuging, and that it is probably a mixture of lipid and globulin, as Dean had already suggested. To these a few more facts can be added:

- (1) That complement is often better when it has stood a few hours than when the blood has been freshly drawn;
- (2) That giving the animal too much anaesthetic destroys its action;
- (3) That it keeps better at room temperature than in an ice incubator;
- (4) That its action is increased by the presence of a trace of either an amino or a fatty acid; preferably glycocoll and oleic acid;
- (5) That no protein, no amino acid, no fatty acid, no triglyceride, no lipid, no salt, nor any combination thereof will restore destroyed complement;
- (6) That lipid solvents destroy complement;
- (7) That alterations of pressure destroy complement;
- (8) That formalin destroys complement.

What light do these facts throw upon the action and being of complement? The fact that it vanishes when kept, suggests that some alteration has taken place in its colloidal particles. From analogy to what takes place in the reagin particles, it is possible that the complement particle is robbed of some of its salts. If correct, then a point is gained in favour of the complement molecule being an adsorptive molecule.

That destruction on keeping is still more probably due to the abstraction of salts, is shown by the fact that complement may be preserved in a concentrated solution of sodium chloride and a 1 in 3 solution of magnesium sulphate, which prevent their abstraction.

That it is thermo-labile points neither here nor there, since a multitude of things may be caused by keeping sera at 57° C. Delicate ferments may be destroyed, the concentration of the free salts may be altered, some lipid-globulin complexes may be split up, an alteration in the concentration of the free fatty acids may ensue, &c.

That when once destroyed it cannot be rejuvenated favours the adsorptive molecule view, since there is something vital in all these lipid-globulin colloidal compounds, as no lipid-globulin complex has as yet been artificially prepared.

That it can be destroyed by shaking, by continued centrifuging, and by altering the pressure at which it is kept, are all points in favour of complement being an adsorptive complex, since these measures are capable of precipitating and hydrolysing such complexes.

That complement is destroyed by giving the animal too much anaesthetic throws additional light upon its nature. Chloroform anaesthesia destroys complement more effectually than ether anaesthesia. Both chloroform and ether are lipid solvents and both have an avidity for oxygen.

Normal sera, when withdrawn while the patient is under deep narcosis, are very liable to give positive Wassermann reactions, owing to the fact that narcosis causes an excess of lipid in the serum (38). Narcotics, then, effect an alteration in lipid molecules. We know that the lipoids largely exist as adsorption complexes with globulin. Therefore, the evidence grows that complement is a lipid-globulin colloidal molecule. From what has just been stated it looks very much as if complement and antibody are similar substances, and I am of the opinion that they are.

Every serum contains lipid-globulin particles, which vary in size. In normal sera these particles are to my mind complement. If the size of these particles be compared, it will be found that they are larger in syphilitic than in normal sera. These particles are, to my mind, complement which has increased the size of its colloidal particles, so as to carry more protective substances to overcome the infection: hence, they become antibody.

If a lipid, such as antigen, is added to a normal serum, the ultra-microscopic particles increase in size, as Jacobsthal (9) was the first to demonstrate; in other words, the complement molecule has taken up a lipid, a phenomenon well known to lipid-globulin complexes.

The ultra-microscopic particles are still further increased in size if the antigen is added to a syphilitic serum, especially if the serum be fresh—i.e. if it contains complement. This signifies that the lipid-globulin in a syphilitic serum has a greater adsorptive capacity than that in a normal serum, which would be natural if it were larger in size; but it also shows that the adsorptive capacity is greater if complement be present. In other words, the adsorptive capacity of a lipid-globulin complex is greatest when the molecules which make up the particles have not been disturbed.

While in the body, the molecules are not likely to be disturbed for long, since the rapidity with which the blood balances a change is phenomenal. This accounts for the failure experienced in differentiating normal from syphilitic sera, by testing them when fresh for their freezing-point, their viscosity, and their hydrogen ion concentration. Soon after the blood is drawn, the vital part of the lipid-globulin vanishes, and its adsorptive capacity diminishes. The

suggestion that complement is the forerunner of antibody does not throw full light upon the active principle of complement.

Since the lipid-globulin complexes are vehicles for oxydases, and since the opinion has been frequently expressed that the Wassermann reaction was of a ferment nature, it struck me that perhaps oxydases played an important rôle in the reaction. If so, then it could only be the complement which held the oxydases, because they are destroyed at 57° C., the temperature at which sera are inactivated, and by alcohol, with which the antigen is prepared.

Several points can be brought forward in favour of complement being the ferment holder, and of the view that the ferment is an oxydase. Physical and chemical factors which destroy ferments destroy complement. Anaesthetics act in virtue of their avidity for oxygen, which they get from both the serum and the cells. Complement gives oxydase reactions, which disappear when complement action vanishes. Although it is highly suggestive that complement action is due to oxydases, no actual proof is forthcoming, since I have failed to replace complement by other oxydase-bearing substances, and all attempts at re-oxygenating inactivated complement have so far met with no success.

Summing up, we see that complement and antibody are the same. They constitute the lipid-globulin of the serum and the size of the particle to some extent determines whether it is complement or antibody. Also, that probably complement acts in virtue of its oxydases, the action of which is primarily to activate adsorption.

Further Proofs and Mode of Action of these Lipoid-Globulin Complexes.

From what has just been stated, certain inferences may be drawn. My biochemical work (23, 30, 32, 34) on the leucocytozoon syphilidis led me to believe that the protective substance, elaborated by the host to overcome the parasite, was lipid-globulin, which carried the ferments (oxydases) which activated the former to destroy the parasite. Complement is also lipid-globulin, to which there is no doubt that oxygen ferments are attached. Complement is, then, the ever-ready or normal resisting substance of every animal, without which the host would doubtless succumb quickly to any disease by which it might be attacked. So long as complement remains complement, it behaves as an oxydase; but when complement is destroyed its oxydase reactions vanish. Therefore, there is some ground for suggesting that the vital part of the lipid-globulin (complement) is an oxydase.

As the existing protective substance is often not powerful enough to overcome the parasite, it is only logical to suppose that the host will increase it in some way. Broadly speaking, one of two things happens when the body is attacked by organisms: either the polymorphonuclear leucocytes or the mononuclear leucocytes are increased. As we are concerned with syphilis, it will only be necessary to dwell upon the latter, since the former play no part in

combating the infection. At the same time, as the mononuclears increase, the protective substance in the serum increases. Sufficient evidence has already been produced to prove that not only is this protective substance lipoid-globulin, but also that it has a cellular origin.

Complement has just been shown to be a lipoid-protein and to be identical with the protective substance, which happens, when it is increased, to be called antibody; therefore, the suggestion at once arises that complement has also a cellular origin. This I have proved to be the case, as an extract of a lymphatic gland will act as complement.

The proofs I have for the statement made, that the colloidal particles are larger in syphilitic than normal sera and that their adsorptive capacity is greater, should now be given. For the colloidal particles to be larger, either one of two things must happen: there must be more protein, or the protein present must be in a less ionized condition—i. e. less colloidal, more like a precipitated protein. That the latter is not the cause can easily be seen, since it would be impossible for the particles to act as protective substances, unless they were in a perfectly colloidal condition and electrically charged.

To prove that the protein was increased in syphilitic sera, I estimated the total nitrogen and found that a higher value could be obtained in syphilitic than normal sera, an observation which Folin had previously made. The increase of nitrogen is, presumably, not entirely protein nitrogen. Some of it doubtless emanates from the lipoid which is attached to the globulin.

Unfortunately, an accurate estimation of the lipoid nitrogen cannot be made, since precipitation of the protein, by alcohol or mercuric chloride, also results in the carrying down of the adsorbed lipoid. Moreover, all the lipoid cannot be extracted with alcohol and ether, while in the adsorbed condition, and any substance which frees the lipoid, hydrolyses the protein to which the lipoid is attached, with the result that amino acids are set free, and, at the same time, the lipoid breaks up, with the result that elementary nitrogen is set free. Although a method could doubtless be devised to estimate the lipoid nitrogen, the amount of lipoid can be better judged by other means, such as by measuring the optical activity and staining properties of the colloidal particles, &c.

By employing these methods it can be shown that there is an excess of lipoid-protein in syphilitic sera; that this protein is a globulin, since lipoids do not form adsorption complexes with albumin; that the lipoid is proved to be in an adsorption complex, since it cannot be entirely removed by ether and alcohol, and that the excess of lipoid is most marked in the late or tertiary cases of syphilis.

This increase of lipoid in late cases of syphilis may be proved in the following ways: The so-called albuminuria of the secondary stage of syphilis may, as is well known, be very pronounced, without there being any clinical signs of kidney disease. If the urine be examined, it will be found that the protein is not albumin, but globulin. The globulin comes from the blood, and not from the kidney cells. The kidney merely acts as a filter, and is not

diseased. Such a urine will give a positive Wassermann reaction. On further examination no blood or casts are demonstrable in the urine; the colloidal particles (globulin) are neither so large nor do they exhibit so pronounced an optical activity as the colloidal particles obtained from a similar urine from a very late case of syphilis. Late syphilitic lesions differ from early syphilitic lesions in that in the former the degeneration of the host's cells is far greater than in the latter, although the number of parasites present is overwhelmingly larger in the latter.

The degeneration is of a lipid nature. To give two examples: if the pyramidal cells of the brain cortex from a case of degenerative encephalitis are examined, it will be found that varying portions of the protoplasm have become finely granular, and that they stain orange to yellow with pyronin. If stained in fresh sections, the granules stain violet with Nile-blue sulphate and orange with sudan III. If the aorta from a case of syphilitic aortitis be examined, masses of lipid material are seen in the walls, and this is never the case in an early and acute endarteritic lesion. For this important observation I am indebted to Dr. Andrewes (33). Moreover, this lipid degeneration is peculiarly localized to the area affected. This excess of lipid doubtless accounts for the deficiency in calcium salts, which Andrewes has observed in his ash analyses of syphilitic aortae.

This strongly suggests that salts have made way for lipoids, as they do in sera, when the lipid-globulin increases in size. This means, then, that larger lipid-globulin molecules exist in the sera from late cases of syphilis than in early cases. The larger the molecule the greater its anticomplementary action. Hence, no relationship exists between the positivity of the reaction and the number of organisms present in the host. The Wassermann reaction is stronger in late syphilitic cases than in early, because there is an excess of lipid.

As lipoids can easily have fatty acid molecules set free from their particles, and as fatty acids may increase the action of complement or, rather, prevent adsorption, this is probably the explanation of the not infrequent occurrence of negative Wassermann reactions in late cases of syphilis, especially when the lesions are limited to vessels. Bisgaard (31) showed that, during death agony, and for some time after, the total nitrogen in the cerebro-spinal fluid was increased and that the main excess was non-protein nitrogen. Those who have worked with the Wassermann reaction have long since been aware that, even in people who have never had syphilis, the blood taken just before death, or just after death, is very liable to give a positive Wassermann reaction.

From these few remarks it will be seen that although the globulin may be partly responsible for the reaction, the lipid is still more so. This statement is still further proved by the fact that, neither the blood nor the urine from a case of non-syphilitic functional albuminuria, in which the protein in the urine is mainly globulin and not albumin, give a positive Wassermann reaction. The reason is because the globulin from such a case has no lipid attached to it,

and that it comes from the glomeruli of the kidneys and is not filtered through from the blood, therefore it is an isoelectric condition.

Having proved that the reagin is a lipid-protein, it must now be explained how it acts. Lipoid-proteins are large molecules. They can be seen when examined ultra-microscopically, i. e. by the dark-ground illumination method. They possess, moreover, strong adsorptive properties and can render soluble, by their presence, a substance which is, under ordinary circumstances, insoluble in a certain medium. Their adsorptive capacity is partly dependent upon, and regulated by, the ions and other groups which are attached to the molecules. Neither pure lipid-globulin nor, still less, pure globulin has a sufficient anti-complementary action to cause as strong a positive reaction as that given by a syphilitic serum. Both pure lipid-globulin and pure globulin are, practically speaking, isoelectric. In their preparation they have been robbed of their ions, and although ions are necessary for the reaction, they only play a subordinate rôle.

I undertook a series of experiments with all the salts that could be supposed to be found in normal serum, and I tested them in various strengths as to their anticomplementary and haemolytic actions, and tested their influence upon the Wassermann's reaction itself. Broadly speaking, all the salts had a strong anti-complementary action, if they were used in much stronger concentrations than those in which they would naturally exist, while in their approximately normal strengths they had neither an anticomplementary nor a haemolytic action, nor did they in any way influence the Wassermann reaction. Therefore, it cannot be the ions themselves upon which the action of reagin depends.

If, then, the adsorptive capacity of the reagin molecule is partly dependent upon its ions, it might be expected that, the larger the molecule, the greater the power with which the ions are attached thereto. The following experiments proved this to be the case. Some lymphatic glands were removed from syphilitic and normal patients, each divided into two portions, dried and weighed. The first portion was incinerated and the chlorides estimated as sodium chloride in the ash. The second portion was thoroughly extracted with alcohol, the alcoholic extracts collected, dried, weighed, and the chloride content determined. The residue of gland substance was then submitted to dialysis and the chlorides estimated in the dialysate. The difference between the two estimations gave the amount of chlorides fixed to the proteins in the tissue under investigation, and this was found to be greater in the syphilitic than in the normal glands. The larger the molecule, not only the greater power of attachment of the ions, but also there will be the more salts in the ionized condition. The proof of this is seen in the greater rapidity for clotting exhibited by syphilitic sera. My friend, Dr. Myers, is at present estimating the amount of calcium in sera, and from the experiments he has already made there appears to be an excess of ionized calcium salts in syphilitic sera.² Those who have

² These last few remarks apply to the early stages of syphilis, because in the late stages the excess of lipoids causes a diminution of the salts. In the so-called tertiary stage, the calcium content of the blood does not vary much from the normal (39).

followed the recent literature on syphilis will remember two papers by Kaplan (26) on the amino content of syphilitic sera.

Estimating the amino acids by Van Slyke's method, Kaplan found that the amino content of syphilitic sera was less than that of normal sera. Kaplan's explanation for the difference was that the syphilitic parasites required a considerable quantity of amino acids for their development, and the serum lost what they used.

Before stating the results I obtained by Van Slyke's method, it would be as well to draw attention to a few points which Van Slyke (27) himself pointed out, before any interpretation is given of the fall of amino acids in syphilitic sera, as mentioned by Kaplan. In Van Slyke's gasometric estimation of the primary aliphatic amino nitrogen, the various kinds of amino derivatives do not give off their nitrogen in the same time. The natural amino acids, i.e. the amino groups which are attached to the carboxyl groups in the α -position, react in five minutes. The ϵ -amino groups in lysin require half an hour; therefore, lysin is the only natural amino acid which requires more than five minutes. Ammonia and methylamine require $1\frac{1}{2}$ –2 hours and urea requires 8 hours. Therefore, these substances can be excluded as having any influence on the results obtained. The same applies to the amino groups in the purin and pyrimidin bodies, which require 2–5 hours before they react. Taking the amino acids individually, Van Slyke found that glycocoll, alanin, valin, leucin, phenylalanin, tyrosin, asparaginic acid, glutaminic acid, and cystin, which only contain α -amino nitrogen, gave up all their nitrogen in five minutes. Lysin takes longer because it contains ϵ -amino groups. Although the guanidin bodies contain nitrogen atoms, they do not react. Arginin contains four nitrogen atoms, but only one reacts, i.e. the nitrogen atom in the α -position. The nitrogen of the indol ring in tryptophane, and of the pyrrolidin rings in prolin and oxyprolin, and of the imidazol nucleus in histidin, does not react; therefore, tryptophane reacts with only half its nitrogen atoms; histidin, with only a third; arginin, with only a quarter; and prolin and oxyprolin do not react at all.

One explanation of the diminution of amino acids in syphilitic sera might easily be that there is a predominance of those which do not react with all their nitrogen. Therefore it would be worth while to undertake a series of experiments to prove if there be an excess of tryptophane, histidin, and arginin in syphilitic sera.

A very important consideration which Kaplan appears to have overlooked is how the amino acids exist in serum. That a few occur free there can be no doubt, as a constant synthesis and analysis of the protein molecules is taking place in the serum. That more occur combined in the protein molecules is also true, because, as Emil Fischer said long ago, proteins are chains consisting of amino-acid links. It will follow from this that the larger the protein molecule, the greater the number of combined amino atoms; therefore, the larger the molecule, the smaller the number of amino atoms which will react

with nitrous acid. Hence, a ready explanation of Kaplan's results would be that the amino nitrogen is less in syphilitic than normal sera, because the protein molecule is larger in the former than the latter.

The proof that the larger the protein molecule the fewer the amino acids which react, is forthcoming from Van Slyke's important observations, that natural proteins only reacted with a trace of their nitrogen, that the albumoses reacted with more, and that the polypeptides reacted with practically all. This proves that the albumoses are degeneration products of proteins, as I have already suggested (23, 24), and it confirms Fischer's theory of the structure of protein, which is, that the smaller the molecule the greater the quantity of nitrogen that exists in the form of free amino acids.

In untreated cases of syphilis, I found, as Kaplan did, that the free amino content was less, but I failed to trace any direct ratio between the free amino content and the result of the Wassermann reaction. If the protein is not precipitated beforehand with alcohol, I found that syphilitic sera, taken from patients who had received no treatment, gave a smaller amino-acid figure than normal sera. But again, no direct ratio existed between the amino-acid content and the result of the Wassermann reaction. As I was more concerned with the study of the protein molecule than with the free amino acids, in the following experiments I did not precipitate the protein with alcohol before testing it by Van Slyke's method. If the amino content of sera, half of which have been kept in an ice incubator, half at room temperature, is tested, the amino content may be either raised or diminished. If raised, the difference is only slight, while if lowered the difference is considerable.

Serum.	Vol. of serum.	Vol. of N collected.	Vol. of N from serum.	Vol. of N from 100 c.c. serum.	Weight of N (mg.) from 100 c.c. serum.
	c.c.	c.c.	c.c.	c.c.	mg.
{ 1. Room temperature	3	3.70	1.85	61.7	71.40
{ 1. Ice incubator	3	4.40	2.20	73.30	84.86
{ 2. Room temperature	3	3.30	1.65	55.00	63.68
{ 2. Ice incubator	3	4.00	2.00	66.60	77.20
{ 3. Room temperature	2	2.70	1.35	67.50	78.10
{ 3. Ice incubator	3	2.90	1.45	48.30	55.90
{ 4. Room temperature	3	4.70	2.35	78.3	90.65
{ 4. Ice incubator	3	2.90	1.45	48.3	55.91
Temperature 19° C.					
Pressure of gas 747 mm.					
Weight of 1 c.c. of N at 19° C. and 747 mm. 1.17 mg.					

The fact that the difference is great when the amino-acid content is lowered, suggests that cold increases the size of the colloidal (protein) molecule. Cold undoubtedly increases reagin formation, as stated before; therefore, there is still more evidence that reagin depends upon the size of the colloidal particle.

The reason why the amino-acid content is sometimes increased in the cold

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is, probably, that fatty acids are thrown out of combination, and they then have the power of liberating some of the amino acids from the protein molecules.

Salvarsan raises the amino content of sera, but the Wassermann reaction may be either positive or negative. The rise begins almost immediately after the injection has been given, and may persist for some weeks.

Serum before '606'.

Vol. of serum.	Vol. of N collected.	Vol. of N from serum.	Vol. of N from 100 c.c.	Weight of N (mg.) from 100 c.c.
c.c.	c.c.	c.c.	c.c.	mg.
2	2.25	1.12	56.25	65.80

Serum one hour after '606'.

3	3.45	1.72	57.5	67.25
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Temperature 15° C.
 Pressure of gas 750 mm.
 Weight of 1 c.c. of N at 15° C. and 750 mm. 1.17 mg.

The addition of fatty acids to sera increases the amino content, especially the addition of oleic acid, which may increase it sevenfold. Triglycerides, on the other hand, considerably depress it. Triglyceride emulsions in sera give very marked positive Wassermann reactions, but fatty acid emulsions may also exhibit a strong anticomplementary action.

Serum (Horse).	Vol. of serum.	Vol. of N collected.	Vol. of N from serum.	Vol. of N from 100 c.c. serum.	Weight of N from 100 c.c. serum.
	c.c.	c.c.	c.c.	c.c.	mg.
I. Stearic acid	1	0.6	0.3	30	35.37
II. Triolein	2	0.2	0.1	5	5.89
III. Oleic acid	2	2.4	1.2	60	70.74
IV. Normal	2	0.4	0.2	10	11.79
V. Protagon	2	0.2	0.1	5	5.89
VI. Tristearin	2	0.2	0.1	5	5.89
VII. Cerebrin	1	0.4	0.2	20	23.58

Temperature 14° C.
 Barometer 763 mm.
 Pressure of gas 751 mm.
 Weight of 1 c.c. of N at 14° × 751 mm. = 1.179 mg.

The explanation of the fact that fatty acids increase, and triglycerides decrease the amino-acid content, is that the amino acids are amphoteric—i. e. they dissociate in an aqueous solution both as bases and as acids. This would make their acid power very weak, and most possibly the fatty acids—weak as they are—relatively stronger. This being so, the stronger acids would tend to replace the weaker, so that the amino acids would be liberated from their compounds, just as, for example, hydrochloric acid would, with a sulphite, form a chloride and liberate sulphurous acid. The triglycerides, being condensation products of glycerol and the fatty acids, would have no acid power, and would not displace the amino acid from their compounds. Barium sulphate raises the amino content, but this may be due to the air which gets into the sera.

Series treated first with barium sulphate.

Serum.	Vol. of serum.	Vol. of N collected.	Vol. of N from serum.	Vol. of N per 100 c.c. serum.	Weight of N from 100 c.c. serum.
	c.c.	c.c.	c.c.	c.c.	mg.
I. Stearic acid	1	1.2	0.6	60	68.7
II. Triolein	2	3.2	1.6	80	91.6
III. Oleic acid	2	1.9	0.95	47.5	54.39
IV. Normal	2	2.2	1.1	55	62.97
V. Protagon	2	2.2	1.1	55	62.97
VI. Tristearin	2	1.4	0.7	35	40.07
VII. Cerebrin	2	1.6	0.8	40	45.8

Formalin markedly decreases the amino content, and all sera which have been treated with formalin have a very strong anticomplementary action.

	Vol. of serum.	Vol. of N	Vol. of N from serum.	Vol. of N from 100 c.c. serum.	Weight of N (mg.) from 100 c.c. serum.
	c.c.	c.c.	c.c.	c.c.	mg.
Serum A alone	3	2.90	1.45	48.30	56.10
Serum A treated with formalin (1 drop 40 % solution to 1 c.c. serum)	3	1.80	0.90	30.00	34.80
Serum B alone	3	4.0	2.00	66.60	77.30
Serum B treated with formalin	2	1.30	0.65	32.70	37.90

Temperature 16° C.
 Pressure of gas 738 mm.
 Weight of 1 c.c. N at 16° C. and 738 mm. = 1.16 mg.

From these few remarks it will be seen that there is no direct ratio between the amino content of the serum and the result of the Wassermann reaction. The decrease of amino nitrogen in syphilitic sera, as shown in Van Slyke's method, is largely owing to the fact that the amino acids are more combined or adsorbed in syphilitic than in normal sera. It does not mean that there are fewer amino acids in syphilitic sera, since, if such sera are hydrolysed, an increase of amino nitrogen is obtained in syphilitic sera.

There is an increase of globulin complexes in syphilitic sera, which means that the protein molecules are bigger; hence the explanation for the diminished amino nitrogen content.

It is interesting here to note the influence which the addition of amino acids to sera had upon the Wassermann reaction. The results of adding amino acids, dissolved in saline, to sera gave some important and interesting results. The three used were tyrosin, leucin, and glycocoll in the strengths of 1 in 1,000, 1 in 10,000, 1 in 100,000, and 1 in 1,000,000. The stronger solutions had an anti-complementary action, and therefore tended to make normal sera positive. Some sera, rich in reagin, became negative. The weak dilutions increased the action of complement, and caused positive sera to become negative: glycocoll had the strongest action in this respect.

If the amino acids are, on the other hand, dissolved in sera, quite different results are obtained. The tendency is for all the sera to become very positive. Should a positive serum containing an amino acid (0.001 per cent.) be added to

another serum the reaction is less positive in the mixture of the sera, one of which contains the amino acid, than in a mixture of the same two sera, to neither of which an amino acid had been added, and this shows that some of the acid has become adsorbed by the lipid-protein molecules of the serum containing no amino acid, and therefore there was less to fix the complement.

If a free fatty acid is present in addition, the activity of the amino acid is markedly increased, and a negative reaction is the result. A stearic acid serum, giving a + + + + reaction, when mixed in equal parts with a glyccoll serum giving a + + + reaction, gives a negative result.

Fatty acids in excess have an anticomplementary action; in weak dilutions they appear to aid complement, or at any rate to inhibit adsorption. Fatty acids frequently cause positive sera to become negative, but if they have been previously added to normal sera, and the fatty acid normal sera are mixed with the positive sera, the reaction usually remains positive, which points to the fact that normal sera can adsorb fatty acids. Normal sera may give positive reactions on the addition of fatty acids, as they did with amino acids. Triglycerides increase the reagin all round, and always give rise to a positive reaction. When in sera they are liable to become split up into fatty acids. This splitting up must be borne in mind, since just sufficient fatty acids may be split off to make the reaction negative.

From these experiments the influence of salvarsan upon the Wassermann reaction can be explained. Salvarsan increases the amino content of syphilitic sera, and this suggests that it breaks up the lipid-globulin (reagin) molecule, a suggestion which is supported by the fact that salvarsan decreases the clotting time of sera; and this would be the case if the calcium salts were split off from the lipid-globulin molecules, thereby diminishing their ionic action. If the molecules are rendered smaller, it would at first sight appear that the Wassermann reaction after salvarsan would always be negative, which is not the case—at any rate, in early syphilis.

If a syphilitic plasmoma be examined histologically, before and after salvarsan treatment, it will be noticed that the protoplasm of the plasma cells in the latter case is completely broken up, but each fragment still retains its chemical and physical properties. If the protoplasm is broken up, the area over which it can act is greater than when the masses are crowded together. Therefore it would appear to be an advantage to break up the reagin particles. Because they are broken up, it does not necessarily follow that each smaller particle does not possess the properties of lipid-globulin. It is only after several injections that actual hydrolysis occurs—i. e., that the lipid fraction is split up into fatty acids, and the globulin fraction into amino acids. So long as the reagin particles are lipid-globulin, they will retain their adsorptive capacity; and as the area over which they act is greater, it will follow that the total action will be increased: i. e. that more complement will be fixed and the Wassermann reaction will be more marked.

As I pointed out two years ago (35), it is only after the first two or three injections of salvarsan that the Wassermann reaction becomes more positive,

and then, after the subsequent injections, it partially diminishes until it becomes negative. Salvarsan at first increases the adsorptive capacity of the reagin molecule, by breaking it up, and then decreases it by causing hydrolysis.

That such an explanation is probably correct is shown by the fact that the increase of the free amino-acid content of the serum is most marked, not after the first three injections of salvarsan, but after the later injections. Often a positive reacting serum—and this is especially the case in the tertiary stage—will become negative after an injection of salvarsan.

In the late cases of syphilis, the lipid portion of the lipid-globulin molecule is greater than it is in the early cases, and the larger the lipid fraction the greater the ease with which a fatty acid molecule is set free.

As stated before, a trace of a free fatty acid will prevent adsorption; an excess will fix complement. Therefore, the first action which salvarsan has in such cases is to set free just sufficient fatty acid from the reagin molecule to readjust complement. Further injections split up the large lipid-globulin molecules into smaller ones, with the result that the reaction will be more positive, and finally hydrolysis occurs, when the reaction becomes negative. Therefore, it at once becomes evident that a negative Wassermann reaction, after treatment, can be no indication as to the number of parasites killed, or as to whether any are left behind or not. The question which now arises is whether there is any specificity in the reagin molecule or whether its action depends entirely upon physical conditions, which are naturally present in syphilis, but which, when brought into play outside the body, can make a normal serum give a positive Wassermann reaction.

The mere fact that an antigen is not absolutely necessary at once rules out the Wassermann reaction as being a specific reaction; but from this it does not necessarily follow that the reagin molecule, when in the body, has no specific action. Further light can be thrown upon this point if Abderhalden's test is considered for a moment. The serum of a pregnant woman will break down placental extract—according to Abderhalden (37)—owing to the presence of a specific proteolytic ferment in the serum. It will necessarily follow that the placental extract for the sera of pregnant women will also be specific. From this it follows that specificity can lie in the peptones, polypeptides, amino acids, or amines. There is a limit to the number of these substances, but there is no limit to specificity. There is also no limit to the variation of the physical configurations of the molecules of the above substances, although there is a limit to their chemical molecular configurations. Therefore, there would appear to be some relationship between specificity and the physical configuration of the foundation molecule upon which are built up the other atoms, which go to constitute the protein molecule. Hence a physical homology exists between the molecules of the serum and those of the placental extract. For the serum of a pregnant woman to break down placental extract, it is necessary that the serum should be fresh, or, in other words, should contain complement.

Interpreted, this means that a serum cannot break down its specific antigen

unless its molecules are ionized and have oxydases attached to them. In the preceding pages it was shown that complement was lipoid-globulin; therefore, it is the lipoid-globulin molecules in the sera of pregnant women which break down the placental extract. Hence, an analogy exists between these molecules and the reagin molecules in syphilitic sera. I have already shown that the action of reagin is one of adsorption. Therefore, on the same principles, there is no reason why adsorption should not take place between the lipoid-globulin particles of the sera of pregnant women and the peptone particles of the placental extract.

Adsorption of homologous molecules results in precipitation, and further dialysis results in hydrolysis. If complement is dialysed its action is destroyed, and it is so, too, with reagin, owing to the fact that the lipoid-globulin molecules split up. In Abderhalden's test, my view is that adsorption between homologous molecules takes place, and this results in their precipitation and subsequent hydrolysis owing to dialysation, which allows sufficient amino acid to get through the fish bladder to give a positive ninhydrin reaction.

At first sight it looks as if the Abderhalden's test is specific, but not infrequently a syphilitic serum from a non-pregnant woman will, with placental extract, give a positive ninhydrin reaction. Therefore, as a test, it can be no more specific than the Wassermann reaction.

The fact that a syphilitic serum will give a positive ninhydrin reaction with placental extract to my mind throws a great deal of light upon both Abderhalden's test and the Wassermann reaction. There is a close similarity between the sera of pregnant women and syphilitic women, because pregnant women seem to be very little affected by—and some even to be immune from—syphilitic symptoms. Moreover, syphilitic sera will give a positive ninhydrin reaction with an extract of almost any organ. Therefore, it looks very much as if neither of these two reactions is specific, but that they are merely group reactions which depend upon certain physical conditions of the protein molecules, and do not necessarily simulate the processes which take place in the body.

There is a marked analogy between the interchange of action between antigen, antibody, and complement, and the interchange of action between sheep's red blood corpuscles, amboceptor, and complement (haemolytic system). Therefore there must be an analogy between the *modus operandi* of Abderhalden's test and of the haemolytic system.

That haemoglobin becomes free when complement and a specific amboceptor are present, is no proof that the red blood corpuscles have been broken down by proteolytic ferments: it is only a proof that the colloidal membrane has been altered by the abstraction of certain chemical groups attached to it, and therefore rendered more pervious by an alteration of the osmotic pressure. Syphilitic sera without any extract at all, provided complement be present, will sometimes give a positive ninhydrin reaction, which can be explained in this way: complement may be fixed by reagin in the Wassermann reaction without there being any antigen present. Owing to the fact that the reagin and complement molecules are homologous, adsorption results and then precipitation. Precipitated

complement is not necessarily destroyed. A ratio exists between the degree of precipitation and the loss of action, since, if the precipitation be only slight, the complement can be re-collected and its action proved by placing it in a haemolytic system.

Should, on the other hand, the complement be precipitated in a dialysing apparatus, hydrolysis of both the complement and the precipitating substance (reagin) takes place, with the result that an excess of amino atoms is formed which dialyses through the fish bladder and gives a positive ninhydrin reaction. Therefore, in the Wassermann reaction we are dealing with a pure precipitation, and in Abderhalden's test with precipitation and hydrolysis.

The proofs for the statements just made are to be found in the following experiments: Colloidal solutions have a surface tension which decreases if the colloidal particles are precipitated. If normal sera are mixed with antigen and complement, and then tested with the stalagmometer, there is no diminution in the surface tension. If syphilitic sera are treated in the same way, there is a diminution of surface tension, and this proves that when reagin, antigen, and complement are mixed, a precipitation occurs, or, in other words, the solution in which they are present becomes less colloidal.

From the above it would appear that there is some relationship between surface tension and the Wassermann reaction; that such is really the case is proved by the fact that the surface tension of sera is lowered by the addition of barium sulphate, Kieselguhr, and formalin, all of which increase the anti-complementary action of sera. The addition of silicic acid or iron hydroxide to sera does not lower the surface tension, and does not cause sera to give a positive Wassermann reaction.

Therefore, there is strong evidence in favour of the precipitation theory for the Wassermann's reaction. The proof that Abderhalden's test is primarily a precipitation and finally a hydrolysis, is shown by the fact that, if fresh syphilitic sera are dialysed, the reagin is partly destroyed and the complement is completely destroyed.

Summary.

It will be seen from what has been stated that once a serum has had its adsorptive capacity increased, as occurs to the lipid-globulin molecules (reagin) in a syphilitic case, it is always liable to exhibit the same phenomenon, should circumstances arise which give it the opportunity.

Most of these opportunities arise only after the blood has been withdrawn. Moreover, it will be seen that several factors may be responsible for a positive reaction—an increase in the size of the protein molecule, an excess of lipid over the protein, a breaking down of the large lipid-globulin molecule into several smaller ones, and an excess of fatty acids and amino acids. These various factors may be at work without the observer's knowledge, and they cannot be

prevented or differentiated; therefore it must be wrong to state that a positive Wassermann reaction is necessarily indicative of active syphilis.

Since a free amino group, or a free fatty acid group, can prevent what would have been a positively reacting serum from giving a positive reaction, it can be easily understood that a negative reaction can neither exclude syphilis nor be taken as an indication of a cure.

It must be obviously incorrect to say that a positive Wassermann reaction means that there are spirochaetae in the body, because, if true, a ratio would exist between the positivity of the reaction and the number of spirochaetae present. This is by no means the case, since the most positive reactions are obtained from those cases which are suffering from diseases caused by syphilis, as the intermediary cutaneous and visceral lymphocytomata, in which no parasites are present, and again in tertiary cases in which only a few parasites are present.

The fact that one may obtain a very strong positive Wassermann reaction in a case of cutaneous lymphocytoma occurring in a patient who has had syphilis, but is, as far as one can tell, cured, throws, to my mind, a great deal of light upon the aetiology of certain chronic dermatoses and even of malignant disease itself.

Once the body has had to form protective substances, should the call upon them have been a prolonged one, in many instances, in spite of the fact that the attacking force has vanished, the body still goes on forming these protective substances, and in an ever-increasing degree, until the protective substances themselves become parasitic, so to speak, upon the host that formed them.

In the case of syphilis, the protective substances are lipoid-globulin complexes which emanate from the lymphocytes. The production of these substances can go on, in spite of the fact that there are no more organisms to vanquish, and in an ever-increasing rate until the lymphocytes are strained to their utmost to furnish these substances, and, in their efforts, they become malignant.

It looks to me as if there is no one cause of the leucaemic and aleucaemic lymphocytomata (36) and malignant disease, but that they are the results of the host's own protection against parasites, &c., of which the leucocytozoon syphilidis is one.

Still further proof in this direction is the degree of positivity which is not infrequently witnessed in sera taken post mortem. As oxydases are quickly destroyed post mortem, and as the sera of some of the late cases of syphilis fail to give oxydase reactions, no ratio can exist between the positivity of the reaction and the oxydase content. Therefore, a strongly positive reaction need not necessarily signify that a grave or widespread active syphilitic condition exists. What applies to the Wassermann reaction, in my opinion, applies to Abderhalden's test. It is not the lipoid-globulin itself which is primarily responsible for the breaking down of the organ. The active agent is the oxydase contained in the complement, which is necessary for the reaction and is linked to the lipoid-globulin, and it is the lipoid-globulin that has the specific stereochemical molecular configuration; the oxydase being non-specific. Further-

more, there is no evidence that the breaking down of the organ is due to a proteolytic or peptolytic ferment. I should not be at all surprised if in time all ferments are found to be oxydases, and that the differences in action rest in the stereo-chemical molecular configuration of the radicles to which the oxydases are attached by means of the ions.

The above points to the fact that the complement is the most important factor in the reaction; therefore, any modification which relies upon the patient's own complement must be fallacious, as the action of the complement is altered by the behaviour of the radicles to which the complement is attached.

Some modifications rely upon the patient's own complement and sheep's blood amboceptor. Results obtained by such modifications must be untrustworthy, since the action of amboceptor upsets its complement action, and vice versa, for both exist in the same molecule. Hence the reason why so many positive reactions are obtained in patients who have never had syphilis. Furthermore, the complementary action of different sera varies enormously; therefore, it is essential that a standardized strength of complement be employed, which means, in other words, that only the original Wassermann reaction is reliable.

Finally, since normal sera will under certain conditions give a positive reaction, any attempt at sharpening the reaction will increase the number of positive results with normal sera; therefore cholesterolized antigens should not be used.

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REFERENCES.

1. Bordet and Gengou, *Ann. de l'Institut Pasteur*, Paris, 1901, xv. 289.
2. Wassermann and Bruck, *Med. Klinik*, Berlin, 1905, i. 1409.
3. Wassermann and Bruck, *Deutsch. med. Woch.*, 1906, xxxii. 449.
4. Fornet and Schereschewsky, *Munch. med. Woch.*, 1907, liv. ii. 1471.
5. Michaelis, *Berl. klin. Woch.*, 1907, xlv. 1477.
6. Porges and Meier, *Wien. klin. Woch.*, 1908, xxi. 206.
7. Klausner, *ibid.*, 214.
8. Schürmann, *Deutsch. med. Woch.*, 1909, xxxv. 616.
9. Jacobsthal, *Munch. med. Woch.*, 1909, lvi. ii. 2607.
10. Levaditi and Yamanouchi, *Compt. rend. de la Soc. de Biol.*, 1907, lxiii. 740.
11. Hecht, *Wien. klin. Woch.*, 1908, xxi. 1742.
12. Fleming, *Lancet*, Lond., 1909, i. 1512.
13. Landsteiner, Müller, and Pötzl, *Wien. klin. Woch.*, 1907, xx. 1421.
14. Sachs, *Berl. klin. Woch.*, 1911, xlviii. ii. 2066.
15. Wechselmann, *Zeitschr. f. Immunitätsforschung*, Jena, 1909, Teil 1, iii. 525.
16. Ascoli, *Munch. med. Woch.*, 1910, lvii. i. 62.
17. Izar, *ibid.*, 182.
18. Lange, *Deutsch. med. Woch.*, 1910, xxxvi. i. 217.
19. Thiele and Embleton, *Lancet*, Lond., 1914, i. 526.
20. Browning, *ibid.*, 740.
21. Mackintosh and Fildes, *Zeitschr. f. Chemotherapie*, Leipz., 1912, i. 79.

22. Rona, Abderhalden's *Handbuch der bioch. Arbeitsmethoden*, Berlin, 1911, i. 328.
23. McDonagh and Mackenzie Wallis, *Biochemical Journal*, Camb., 1913, vii. 517.
24. Wassermann and Lange, *Berl. klin. Woch.*, 1914, li. i. 527.
25. Mantovani, *Giorn. Ital. d. Malat. vener.*, ed. Pelle, lv. 759.
26. Kaplan, *New York Med. Journ.*, New York, 1913, xcvi. 1172; xcvi. 157.
27. Van Slyke, Abderhalden's *Handbuch der bioch. Arbeitsmethoden*, Berlin, 1912, ii. 995.
28. Landsteiner and Rock, *Zeitschr. f. Immunitätsforschung*, Jena, 1912, Teil 1, xiv. 14.
29. McDonagh, *West London Med. Journ.*, 1914, xix. 1.
30. McDonagh, *A Report upon the Biology of Syphilis* (Harrison and Sons, London), 1914.
31. Bisgaard, *Biochem. Zeitschr.*, Berlin, 1914, lviii. 1.
32. McDonagh, *Archiv f. Derm. u. Syph.*, 1914, cxix. 205.
33. Andrewes, *Local Gov. Board. Report of the Medical Officer*, 1914.
34. McDonagh, *Archiv f. Derm. u. Syph.*, 1914, cxx. 289.
35. McDonagh, *Brit. Med. Journ.*, 1912, i. 1287.
36. McDonagh, *Brit. Journ. of Dermatology*, 1914, pp. 283 and 337.
37. Abderhalden, *Abwehrfermente*, vierte Auflage (Verlag von J. Springer, Berlin), 1914.
38. Nerking, *Munch. med. Woch.*, 1909, lvi. ii. 1475.
39. Myers, *Lancet*, 1914, ii. 767.

THE METABOLISM OF NITROGEN IN DERMATOSES

GENERAL REVIEW

By H. L. TIDY

Introduction.

A LARGE portion of the investigations of the metabolism in dermatoses has been directed towards the partition of nitrogen in the urine. Reference may be made briefly to what is known on the variations of the partition in normal persons. Previous to 1905, it was known that changes in the constituents of the diet altered the partition of nitrogen. This was mainly based on the excretion of uric acid and its ratio to urea. Thus Weintraud (1) and Umber (2) observed that the excretion of uric acid on a diet including thymus was double that on an ordinary protein diet containing an equal amount of nitrogen. Folin (3) in 1905 proved that the partition of nitrogen varied greatly with the amount of nitrogen excreted, so that it is affected by the quantity of the nitrogen in the food as well as by qualitative changes in the constituents of the diet. Table I is compiled from Folin's analyses and shows the partition of nitrogen for various daily amounts of urinary nitrogen, the diet being purin free.

TABLE I.

Total N in Urine (gm.).	Excretion per cent. of total N.					
	Urea N.	Ammonia N.	Urea N + Ammonia N.	Uric Acid N.	Kreatinin N.	Undeter- mined N.
3	60.7	8.5	69.2	3.1	14.8	12.9
4	67.0	8.7	75.7	2.5	12.4	9.4
5	72.7	7.2	79.9	2.	10.3	7.8
6	76.8	4.5	81.3	2.1	8.3	8.3
7	77.8	4.6	82.4	1.8	7.4	8.4
8	80.0	4.7	84.7	1.7	6.4	7.2
9	80.7	4.7	85.4	1.5	6.0	7.1
10	81.6	3.8	85.4	1.6	6.0	7.0
11	82.5	3.9	86.4	1.5	4.9	7.2
12	83.3	3.7	87.	1.4	5.0	6.6
13	85.7	3.	88.7	1.4	4.3	5.6
14	86.7	3.8	90.5	1.1	3.6	4.8
15	86.9	3.7	90.6	1.1	3.9	4.4

Ignorance of this important factor has led to many unjustifiable deductions from analyses performed previous to 1905. Burian and Schur (4) in 1900 had shown that the urinary uric acid was partly endogenous, being derived from

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tissue metabolism, and partly exogenous, being derived from the food. Folin extended this theory of an endogenous and exogenous metabolism.

Several of the researches on dermatoses have been performed with diets containing purins, and it is therefore important to know the excretion of uric acid on an unrestricted diet. Seven physiologists (5) at University College, London, found as the mean of their analyses that the uric acid nitrogen formed 1.54 per cent. of the total nitrogen. Maillard (6) found 1.43 per cent. in the urine of French soldiers. The figure 1.5 per cent. may be accepted for the excretion of normal persons on a mixed diet.

With regard to the nitrogen which is lost from the surface of the skin, there is general agreement that, apart from visible perspiration, this does not exceed a few decigrammes daily. The most careful experiments are perhaps those of Schwenkenbecher and Spitta (7). They decided that for a man of 70 kilogrammes leading an ordinary life the loss of nitrogen by the skin was about one-third of a gramme daily.

Early Researches.

The connexion of certain conditions of the skin with gastro-intestinal disturbances is so obvious that it has been recognized from very early times. Thus in some people erythema and urticaria follow the ingestion of certain fruit, fish, or other articles of diet. On this basis of truth at one time or another every general disease of the skin and probably every local condition has been ascribed to intestinal changes. These views led to the examination of the urine in order to obtain definite evidence of abnormalities of metabolism. The earlier investigators usually confined themselves to estimating the daily excretion of urine. Researches subsequent to 1888 will be considered, firstly, because they are continually being quoted, often inaccurately, and secondly, because they show how views have developed on the connexion between dermatoses and errors of metabolism.

Tenneson and Lyon (8) in 1888 examined the urine daily in two severe cases of dermatitis herpetiformis over a period of several months. The only qualitative analysis was that of urea. The daily excretion of urea nitrogen varied between 5.8 and 3.0 gm. daily. The urea was observed to fall to its lowest point before the occurrence of a relapse. This happened on many occasions. There is no statement of the diet, or the weight of the patient. In the second case the excretion of urea nitrogen varied between 9.3 gm. and 5.7 gm. The relation of the variations to relapses was not very definite. It is noticeable that the excretion of urea in the first case fell to a very low point. The amount is actually less than is passed by human beings in complete starvation. It is on this deficient excretion of urea that so many theories of auto-intoxication have been based. A second point to notice is a statement that the urea fell to its lowest point before an exacerbation of the eruption.

There has been much discussion on this point, and it will be referred to again.

Bar and Tissier (9) examined the excretion of urea in the case of a woman in whom dermatitis herpetiformis developed in three successive pregnancies. Like Tenneson and Lyon they found that the urea fell to a minimum at the onset of an exacerbation and then rose again. The patient had definite albuminuria and is said to have had nephritis. On these analyses the theory is frequently based by subsequent writers that dermatitis herpetiformis is a cutaneous form of uraemia. This was disputed by a school which held that the origin was nervous, and in support of this Gaucher and Claude (10) published some analyses. In their case there was no albuminuria, and as this has been found in many similar cases we may here dismiss the theory of cutaneous uraemia, although this does not necessarily negative the possibility of a connexion between dermatitis and some renal abnormality. Gaucher and Claude also claim that their analyses show that the excretion of urea is increased at the onset of an attack, but an examination of their analyses reveals nothing to support this claim, as their patient had no relapses and only one analysis was made during the attack.

Mention may be made of three Paris theses published in the year 1895 by Wilenski, Perrin, and Thilliez (11, 12, 13) on various aspects of dermatitis herpetiformis. The two latter need not be further referred to, but the thesis of Wilenski is based on an exhaustive search of the literature up to that date and his conclusions may be considered to reflect the opinions held in France at that time. He arrived at the following conclusions:

- (1) Marked diminution in the excretion of urea is very frequent.
- (2) In certain cases albuminuria occurs.
- (3) This albuminuria is due to a chronic nephritis, which advances parallel with the dermatitis. The two conditions, nephritis and dermatitis, are due to one general cause, this being 'Arthritism'.
- (4) The diminution in the excretion of urea is probably the consequence of renal insufficiency, and of a disturbance of nutrition, both resulting from the arthritism.
- (5) The condition of arthritism leads to the changes in the skin in the following manner. Owing to the disturbance in nutrition excretory products accumulate in the system, and these through the central nervous system produce the cutaneous lesions of dermatitis herpetiformis.

The thesis contains a full bibliography of estimations of urea up to that time, but gives no definition of arthritism. We may perhaps say that the theory of arthritism has been replaced by that of auto-intoxication. It is a process which nobody understands, but which explains everything.

A few investigations may be briefly referred to. Leredde (14) in dermatitis herpetiformis found great oscillations in the excretion of urea. Pini (15) in a case of pemphigus vegetans found a diminution of urea. Audry Gerard and

Dalons (16) in a case of true chronic pemphigus found great variations in the excretion of urea, and they also noticed an increase in the excretion of uric acid, an observation which is apparently first noticed here, and which becomes of importance in the consideration of more recent work. Allgeyer (17) in two cases of dermatitis herpetiformis found the urea was sometimes above and sometimes below normal and sometimes normal.

The interest of this last work is that it reflects the official German view. The work to which we have referred so far has been exclusively French. It has always been the French School which has supported the view that cutaneous diseases are due to internal disturbances, and has consequently attempted to support this by examinations of the urine. The German and Viennese Schools, influenced greatly by Hebra, have consistently denied the connexion and hold that a cutaneous manifestation is simply a disorder of the skin.

Hardouin (18) in 1900 examined the urea excretion over many months in two cases of dermatitis herpetiformis. He arrived at the conclusion that 'there is a constant relation between the variations in the amount of urea and the exacerbations of the eruption'. Both his cases showed a periodicity in the urea excretion and each period corresponded to an outbreak. The relation of the outbreak to the excretion is not the same in the two cases. In the second case the eruption occurred when the urea excretion was at its lowest, while in the first case the eruption did not occur until the urea had risen considerably above its minimum. In both instances the minimum was about 4 grm. of urea nitrogen. Hardouin gives no details of diet or weight of the patient, and the possibility cannot be excluded that the periodicity of the urea was due to the patient gaining weight between the attacks and consequently retaining nitrogen. Hardouin arrives at the conclusion, previously expressed by Tenneson and Lyon and other writers, that a relapse is preceded by a period of deficient excretion of nitrogen.

So far there has been a great similarity between the various investigations. They have been confined almost entirely to estimations of urea performed by French workers in cases of dermatitis herpetiformis. The theory has been repeatedly advanced by the authors that deficient excretion of urea must involve a retention of toxic substances in the body, the presence of which lead to the cutaneous condition. The analyses almost without exception have shown a low excretion of urea, which has supported the theory of retention.

From about the year 1900 other nationalities take up this work and investigate different conditions, and, further, they work on a different basis. The general idea appears to be that toxic substances are formed during the metabolism of protein, and these toxic substances are the cause of the eruption. The greater the amount of protein disintegrated, the greater will be the amount of toxins produced. Hence in cutaneous disorders they expect to find evidences of an abnormally high metabolism of protein, which would be shown by an increased excretion of nitrogen. This is the direct opposite of the French view of 'Hypoazoturia' or diminished excretion of nitrogen. The French held that

the amount of toxin formed was normal, but the excretion was deficient and hence toxins were retained in the body. The German and other schools wished to prove that an abnormal formation of toxin occurred and the presence of this increase leads to the pathological condition of the skin.

The first experimenter on these lines is probably Stüve (19), who investigated a case of pemphigus vegetans to ascertain if any pathological increase occurred in the disintegration of protein. The analyses were carried out on seven consecutive days, during which the diet was carefully measured and its nitrogen content estimated. The diet consisted of milk, eggs, bread, butter, and asparagus, and contained 20.08 grm. of nitrogen daily. The daily excretion (stated in grammes) was as follows:

Urine.					
Nitrogen in Food.	Total N.	Uric Acid N.	N in Faeces.	Total N excreted.	Uric Acid N %.
20.08	17.34	0.37	1.6	18.94	2.1

These figures are the average for a period of seven days. French experimenters had, and unfortunately still adhere to, a plan of giving specimen analyses during a period and not the mean and total figures. For this reason it is often impossible to draw any conclusions from their published results.

Now from Stüve's figures it will be seen that the patient excreted one gramme of nitrogen daily less than the amount in the food, which was not the result which the experimenter expected. For this he gives several reasons. Firstly, the diet is very rich in nitrogen, and the retention of one gramme daily is approximately what would be found in a healthy individual. This is undoubtedly true, and it may be said that without any other information the figures for nitrogen would be regarded as normal for a healthy person, except that the uric acid is high, possibly as the result of asparagus being given.

Secondly, Stüve argues that there are two factors present which would lead one to expect a great retention of nitrogen, these factors being a large and obvious excretion of albuminous fluid from the wounds, and a marked loss of weight, the patient having lost three kilogrammes in the period. To balance these factors leading to a retention of nitrogen, there must be a factor causing an increased excretion of nitrogen, and hence Stüve concludes that in pemphigus vegetans there is an abnormal destruction of protein. This is the conclusion which Stüve desired to establish.

Unfortunately there appears to be a false step in this reasoning, since a marked loss of weight is associated with an increase in the excretion of nitrogen and not with a diminution. Probably the two factors, loss of body weight and loss of albuminous fluid from the wounds, roughly balanced each other and hence the analyses were within normal limits. For the time being Stüve was considered by many authorities to have proved his contention.

The next experiments to which reference may be made were carried out by Radaeli (20), in Italy, on a series of cases of lichen planus. They were undertaken with the same expectation as Stüve's, namely, that an increased excretion of nitrogen would be found. Clinically the cases were all severe, but there was no pyrexia.

The results of the analyses are given in Table II, the figures given being the average for the period.

TABLE II.

Case.	Duration.	N in Food. gram.	Urine.			Faeces. Total N.	N Balance.
			Total N. gram.	Urea N. gram.	Urea N. %.		
1	6 days	22.21	19.23	17.83	87.5	2.84	+ 0.14
2	9 days	21.77	17.21	15.27	88.7	2.66	+ 1.90
3	11 days	19.55	17.69	15.36	86.8	2.03	- 0.17
4	9 days	16.61	17.57	13.92	79.2	2.56	- 3.52

In Cases 1, 2, and 3, the figures are within normal limits. In Case 4 there is an excessive excretion of nitrogen. Radaeli suggests no explanation of this, but does not consider that his results support the view of an increased protein metabolism.

In 1903 Radaeli (21) published a long investigation on the metabolism in various forms of 'pemphigus and pemphigoid conditions'. Radaeli apparently felt that his previous work on lichen planus had not established his view that in general cutaneous conditions the metabolism should show an increased destruction of protein, and hence a loss of nitrogen by the body. The analyses on this series of cases were undertaken to see whether pemphigus and bullous eruptions would show the increase of nitrogen excretion. Consequently in many of his cases the urinary analyses were carried out while the eruption was quiescent, since, according to the theory on which he was working, the constitutional disturbance should still be present. As a result, many of the analyses show nothing abnormal. Table III has been abstracted from his work and shows all the analyses of interest.

TABLE III.

Case.	Age.	Duration.	N in Food.	Urine. Total N.	Faeces. Total N.	N Balance.
1	12	8 days	10.02	8.83	0.98	+ 0.22
5	75	10 days	10.65	7.06	0.83	+ 2.76
7	5	7 days	10.73	8.07	1.12	+ 1.51
8	16	7 days	15.63	12.27	1.44	+ 1.91
13	38					
Period 1		9 days	13.54	9.13	1.19	+ 3.25
Period 2		9 days	13.51	11.09	1.04	+ 1.38
Period 3		13 days	13.52	12.39	1.11	+ 0.01
15	47	7 days	17.71	14.90	1.39	+ 1.42

Certain special points may be referred to.

Case 1 was a patient with dermatitis herpetiformis. During the period of investigation the eruption was quiescent. The analyses show nitrogenous

equilibrium. The special interest of this is that a recurrence followed immediately, and thus the relapse was not preceded by the period of diminished excretion of urea or nitrogen, which has been referred to by previous workers.

In *Cases V, VII, and VIII* there is distinct retention of nitrogen, which is contrary to the result which Radaeli expected. In *Case XV*, a patient with pemphigus, the eruption was abundant, and Radaeli considers that the retention of nitrogen is insufficient to account for the loss from the skin, and thus the analyses point to a somewhat increased decomposition of tissue protein. In the light of our present knowledge it seems fair to say that these cases are within normal limits, with the exception of *Case V*, a man of 75 years of age, who died from arterio-sclerosis one month later.

In *Case XIII* analyses were carried out during three phases of the eruption. It will be seen that the retention of nitrogen corresponds to the severity of the eruption, and disappears when the patient becomes convalescent. This is the first case in the literature where this relation is scientifically established.

Radaeli did not consider that the analysis justified the conclusion that an increased disintegration of tissue protein constantly occurred during these cutaneous lesions. He believed that the large amount of nitrogen retained in *Case XIII* is explained by an abnormal loss through the skin.

The use of the term 'retention of nitrogen' in reference to these and subsequent researches may be explained here. The retention of nitrogen is estimated by the difference between the amount of nitrogen ingested in the food and the amount which passes out of the body in the excreta. In ordinary experiments on metabolism these excreta are the urine and faeces, and the small amount lost through the skin is considered to be negligible. Hence 'retention' is used for the difference between the nitrogen of the food and that excreted in the urine and faeces. The term is used here with the same meaning, but it is not justifiable to assume that such nitrogen is being actually accumulated in the system, as in dermatoses the amount of nitrogen lost through the skin may be several grammes daily.

The conclusions of Radaeli are supported by the analyses in a severe case of pemphigus foliaceus which were carried out by Selenew (22) in 1905. In addition to measuring the excretion in the urine and faeces, the scales were also collected during the period of investigation as far as possible and their nitrogen content estimated.

Table IV gives the daily average in grammes for each period.

TABLE IV.

Case.	Duration.	N in Food (grm.).	Total N. Urine.	Total N. Faeces.	N in Scales.	N Balance.
1	6 days	28.0	14.5	3.5	5.1	+4.9
2	7 days	28.8	14.7	3.9	4.7	+5.5

An interval of eighteen days elapsed between the two periods.

It will be seen that there is a difference of 10 grm. daily between the nitrogen in the diet and the nitrogen in the usual paths of excretion, the urine and faeces. Even when the nitrogen in the scales is allowed for there is still a large retention. Selenew considers that this is accounted for by the serum and scales which escaped estimation. Unfortunately Selenew made an obvious

error in giving a diet containing such an abnormal amount of nitrogen, the inability of the patient to deal with it being shown by the quantity of nitrogen excreted by the faeces.

An article published in 1904 by Gaucher and Desmoulières (23) may be referred to. These authors express the view that eczema and psoriasis are variations of the same lesion. In accordance with this they found the urinary analyses to be similar in the two conditions, the characteristics being a low excretion of nitrogen, with a diminished proportion of urea nitrogen. From this they argue that there is an incomplete katalysis of protein, and consequently an excessive production of extractives. They conclude that in these two conditions an 'auto-intoxicational diathesis' is present.

This article was replied to by Brocq, Desgrez, and Aygnac (24). They desired to show that in psoriasis there was no characteristic change in the urine. So long as the disease was present, the extent of the eruption did not concern them. Hence the eruption varied greatly in different cases, but the authors made no statement on the condition of the patients during the periods of analysis. Most of the results are absolutely normal. The authors believe this proves their contention, but it is perhaps more accurate to say that the analyses prove nothing at all.

These two articles have been referred to not on account of their importance, but because they mark the end of the old French School which for so long practically had this question to themselves. The researches were generally confined to a few estimations of urea. No attention was paid to diet, pyrexia, changes in weight, or any other factor. Domestic statements were based on the flimsiest evidence.

At this time, in the year 1906, Folin published his investigations on nitrogenous metabolism in healthy individuals on various diets. It became obvious that experiments on metabolism must be carried out with great care before any conclusions at all can be drawn from them. Perhaps as a result of this being realized no important communication was published for nearly four years.

Considering the position in 1906, the results obtained and the various theories advanced may be recounted: First, it had been held that the excretion of urea in general dermatitis was constantly below normal. This result was obtained by numerous workers. On this diminished urea excretion the theory was founded that certain diseases of the skin were due to retention of nitrogen. This was the prevailing theory of the French School which ascribed all diseases of the skin to the hypothetical 'arthritis', a theory based to a great extent on the cutaneous lesions connected with gout.

Secondly, it was said that the percentage of urea nitrogen to total nitrogen was lower than normal in certain conditions. On this a theory was based that the metabolism of protein was incomplete, that the amount of extractives formed was higher than normal, and that the presence of these extractives led to the cutaneous lesions. This is practically a later elaboration of the first theory and

was held by those more advanced researchers who had abandoned 'arthritis' for 'auto-intoxication'.

Thirdly, from the time of the earliest researches it was stated that the excretion of urea was most deficient previous to an outbreak or a relapse and then rose again during the eruption. This contention was supported apparently by several investigations. It was held to prove that the condition of the skin was the result of the disturbance of metabolism.

Fourthly, shortly before the end of the period a theory rose that in general dermatoses it might be expected that the protein metabolism would be greater than normal. It was argued that the excessive disintegration would lead to an excessive production of toxins by which the cutaneous lesions would be caused. The body would therefore be expected to excrete more nitrogen than it received. The researches performed with this idea were carefully carried out and produced no evidence in its support.

An impartial critic at this date might have decided that there was sufficient evidence to prove that a deficient excretion of urea and nitrogen occurred in general dermatoses during the eruption, and that there was considerable evidence that this abnormality was present before the appearance of the eruption.

The questions which arise during consideration of subsequent researches may be stated here: (1) Is the total excretion of nitrogen deficient by the ordinary paths, that is, by the urine and faeces? (2) Is the excretion of urea or uric acid abnormal, either in absolute amount or relatively to the total nitrogen? (3) Are such changes as occur characteristic of any special form of dermatitis? (4) What is the cause of these changes?

Recent Researches.

The first investigation to be considered is a research by Johnston and Schwartz (25) on 'The Metabolism of Certain Skin Disorders'. Three groups of cases were examined: (1) Erythema and urticaria, (2) bullous eruptions, and (3) scaling eruptions.

Certain general conclusions affected all groups. A trace of albumin was present in about one-third of the cases, distributed over the three groups. The albumin disappeared in those cases in which recovery occurred, with the exception of two patients suffering from definite nephritis. Indican was found to be very variable in amount and bore no relation to the severity of the eruption and gastro-intestinal disturbances. No connexion could be traced between the eruption and the amount of indican.

Unfortunately the nitrogen in the diet was not measured. From the analyses of the nitrogenous excretion the authors drew the following conclusions: (1) The most definite variations in the partition of nitrogen occur in the prodromal period of an eruption or previous to a relapse. (2) The disorder of

metabolism most frequent is failure of urea synthesis, resulting in a decided drop in the excretion of urea, and a low percentage compared to the total nitrogen.

With regard to the second conclusion, a low percentage of urea nitrogen does not justify the assumption that there is failure of synthesis of urea.

The first conclusion has been suggested by previous writers. The evidence in support of it is perhaps more definite in this article than in others. It rests mainly on three cases with bullous eruptions. Analyses in the remaining cases are not sufficiently extensive to give assistance. Even in the three cases the fact that the urine was examined not daily, but at irregular intervals, makes it very difficult to be certain of the course of the metabolism.

In one case of dermatitis herpetiformis two relapses occurred, both of which were preceded by periods of low relative urea excretion. The analyses show two other periods of low urea excretion, which were not followed by relapses. In another case of dermatitis herpetiformis three relapses occurred, in one of which the urine was not examined. The other two relapses were associated with low percentages of urea nitrogen. Other periods with equally low percentages were not followed by relapses. In a third case an eruption developed on the scrotum of a patient already suffering from a widely distributed dermatitis herpetiformis. On the day of the eruption the urea nitrogen formed 62 per cent. of the total nitrogen, an exceptionally low proportion in view of the fact that the total nitrogen amounted to 9 grm.

The possibility of several fallacies cannot be excluded. Thus the treatment included sweat baths, which would influence the urinary secretion. Although they cannot be considered to prove it, yet the analyses are consistent with the view that relapses are preceded by periods of low urea excretion.

Table V contains the analyses of a period which was followed by a relapse.

TABLE V.

Date.	Total N in Urine (grm.).	Urea N. %	
May 24	12.24	85.3	
May 28	11.5	77.0	
May 31	11.0	72.7	Recrudescence
June 4	11.8	85.1	

Unfortunately the investigations which remain to be considered produce no evidence on this particular question. The subject will be referred to later.

Schamberg and others (26) published very full researches on 'Protein Metabolism in Psoriasis' in 1913. The authors arrive at the following conclusions: (1) Patients suffering from psoriasis exhibit a remarkable retention of nitrogen. This retention appears to be proportional in a general way to the extent and severity of the eruption. (2) The nitrogen is retained and stored in the system. (3) The retention of nitrogen is not always associated with a corresponding gain in body weight. (4) The nitrogen is retained to a greater

extent than has been observed in any other condition, and the retention occurs on a diet on which a normal person would fail to maintain nitrogenous equilibrium. On a full diet the retention may be as much as 11 grm. of nitrogen daily. (5) The retention is not due to any renal disturbance. (6) The retention in most cases is greater than could be accounted for by the protein lost in the scales. (7) The retention persists in some cases after scaling has ceased.

Briefly stated, these conclusions suggest that a patient suffering from psoriasis can store nitrogen to the extent of many grammes daily without any gain in body weight and without any deficiency in the renal functions, and that this storage is peculiar to psoriasis.

Table VI illustrates the results obtained at one period with a certain subject.

TABLE VI

Date.	Total N.	Urea N.	Urea N (% of Total N).	N in Faeces.	Total N excreted in Urine and Faeces.	N in Food.	N Balance.
1913.							
Jan. 1	3.39	2.17	64.0	1.01	4.40	6.71	+ 2.31
" 2	3.16	2.04	64.7	1.01	4.17	6.93	+ 2.76
" 3	3.30	2.05	62.2	1.01	4.31	6.76	+ 2.45
" 4	3.24	2.04	63.0	1.01	4.25	6.56	+ 2.31
" 5	3.28	2.46	75.0	1.01	4.29	6.36	+ 2.06
" 6	10.94	9.48	86.6	1.01	11.95	16.83	+ 4.88
" 7	4.81	3.60	74.9	1.01	5.82	6.61	+ 0.79
" 8	3.42	2.36	69.1	1.01	4.43	8.44	+ 4.01
Average	3.30	2.19		1.01	4.31	6.98	+ 2.67

At this period the patient was taking a very low protein diet, containing less than 7 grm. of nitrogen. Yet the retention of nitrogen is more than 2.5 grm. daily. (The excretion on January 6 and 7 is explained below.) On larger diets this patient retained about 5 grm. a day. The investigation of this case was very full and during several months on varying diets this retention was present. For example, in another period the diet contained 11.9 grm. of nitrogen, while the urine contained 6.3 and the faeces 0.7, the retention being thus 4.5 grm. daily. In the other cases investigated there was a similar retention, and the first conclusion of the authors may be accepted as proved by the analyses.

The next question is whether the retention of nitrogen is associated with a corresponding gain in body weight. A person who is gaining weight rapidly over a long period, for example after an acute illness, will necessarily show a large retention of nitrogen (see Table VIII, Control No. 3). On examining the weight of the patient already referred to, it is found to have fallen 1.2 kilos during three months. In this time the retention of nitrogen amounted to 350 grm., which corresponds to nearly 2.5 kilos of protein. The accumulation of this quantity of protein would be associated with a much greater gain in body weight, since it may be assumed that an increase in fluid would also occur.

Similar results were obtained in other cases of psoriasis, and the conclusion can be accepted that the retention of nitrogen is not necessarily associated with a corresponding gain in body weight.

Nor is there any doubt that retention of nitrogen occurred on a diet in which a normal individual would lose nitrogen rapidly. Thus in one period the patient took a diet containing 4.4 gm. of nitrogen and less than 40 calories per kilo body weight, and retained 0.5 gm. nitrogen daily. In order to maintain equilibrium on a low protein diet the number of calories must be far higher than this, and an ordinary individual would undoubtedly have lost nitrogen rapidly on this diet. Graham (7*a*) in some recent researches lost nitrogen rapidly on a diet containing 12 gm. of nitrogen and 32 calories per kilo.

Obviously, these patients with psoriasis can retain nitrogen on a diet in which a normal person would fail to maintain equilibrium.

The authors produce evidence that the retention of nitrogen is not due to any disturbance of the renal function or to inability to excrete nitrogen. It will be seen on reference to Table VI that the excretion of nitrogen was much higher on two days. This increase was due to the fact that 20 gm. of urea were administered. Twenty grammes of urea contain 9.3 gm. of nitrogen, and the urine in the forty-eight hours following shows an increased excretion of nitrogen of approximately this amount. Apparently there is no inability on the part of the kidney to excrete urea.

The authors believe that the analyses point to retention continuing after the scaling has disappeared, but they state definitely that they do not consider that the analyses absolutely prove this. It is difficult to examine the analyses from this point of view. Some of the patients, who numbered six in all, had not recovered from the eruption when the analyses were discontinued. The tendency of a patient to gain weight during convalescence also causes complication. The authors frequently kept the patients on very low diets for the purposes of investigation. Thus one adult patient was kept for many weeks on a diet containing less than 7 gm. of nitrogen daily and of low value in calories. She lost weight during this period and, as might be expected, retained nitrogen and gained weight rapidly when placed on a full diet during convalescence.

Further, the retention of nitrogen runs roughly parallel to the severity of the eruption, and consequently only a small retention could be expected after the scaling has ceased. It is impossible to draw conclusions from small retentions of nitrogen unless the diet is such that a normal individual would excrete more than he ingested. None of the authors' cases quite fulfil the necessary conditions during convalescence. Certainly the analyses contain no proof that retention can occur in the absence of scaling, but we may agree that there are one or two suggestive periods.

We have considered and agreed with the following conclusions: (1) Patients suffering from psoriasis exhibit a marked retention of nitrogen, which is roughly proportional to the severity of the eruption. (2) The retention is not associated with a corresponding gain in weight, nor is it due to disturbance of renal

function. (3) The retention occurs on a diet on which a normal person would lose nitrogen.

We have still to consider the following questions: (1) Does this retention occur only in psoriasis? (2) Is the nitrogen balance actually accumulated in the system? (3) Is the retention only apparent and explained by protein shed in the scales?

We shall leave these questions until we have referred to some analyses carried out on three cases of exfoliative dermatitis in the London Hospital (27).

The patients in all cases were taking a mixed diet containing meat, that is to say, it was not purin free.

Table VII gives the daily analyses for a short period in a severe case of primary erythrodermia. It will be seen that the excretion of nitrogen in the urine is very low compared to the nitrogen in the food. The diet had a value of about 3,000 calories. Yet the urinary nitrogen fell to under 3 grm. Table VIII gives the mean of the analyses for various periods (Case 1).

Obviously there is an enormous retention of nitrogen occurring over many months.

A recurrent erythrodermia (Case 11) shows the same results although the excretion of nitrogen in the urine did not fall to such low figures. This patient improved rapidly during the period of analysis and the change is reflected in the results. The excretion of urinary nitrogen and the percentage of urea nitrogen rise during successive weeks. Thus the retention of nitrogen is related to the severity of the eruptions.

It will be seen from Table VIII that, during the period January to November, Case 1 increased in weight a little more than 3 kilogrammes. It is not extravagant to assume that the daily retention of nitrogen was 4 grm. This would correspond to $7\frac{1}{2}$ kilogrammes of protein in ten months, and the addition of this to the system would also necessitate a considerable increase in fluid. The retention is therefore not associated with a corresponding gain in body weight.

It will be seen that in these two cases of erythrodermia, the same phenomenon of retention occurs as in the patients with psoriasis. Also it can be recognized in a case of dermatitis herpetiformis recorded by Radaeli in 1903 and in a case of pemphigus foliaceus recorded by Selenew in 1905.

It is obvious that retention of nitrogen is not peculiar to any one form of dermatitis. It is probable that it would be found to occur in all conditions in which the skin is widely affected by inflammatory or proliferative conditions.

The fate of the retained nitrogen will now be considered. The explanation must be independent of any one disease of the skin. There are several possibilities: (1) A true storage of nitrogen occurs in the body. Schamberg and his co-workers on psoriasis believe this to be the explanation. They consider that the growth and proliferation of the epithelial cells of the skin removes an enormous amount of protein, or its constituent parts, from the circulation and

TABLE VII
N in Urine (gram.).

	N in Food (gram.).	Total N.	N in Urine (gram.).				Partition of N.			
			Urea N.	Ammonia N.	Uric Acid N.	Unde- termined N.	Urea.	Ammonia.	Urea + Ammonia.	Uric Acid. Unde- termined.
January 23rd	12.03	8.50	5.86	0.25	0.50	1.89	68.9	2.9	71.8	22.3
25th	13.55	6.11	4.24	0.26	0.37	1.24	69.4	4.3	73.7	20.2
26th	12.17	8.52	5.89	0.22	0.44	1.97	69.1	2.6	71.7	23.1
27th	10.66	4.52	2.80	0.26	0.43	1.03	61.9	5.8	67.7	22.8
28th	15.54	2.88	1.66	0.16	0.25	0.81	57.6	5.6	63.2	28.2
February 1st	11.48	3.08	2.16	0.12	0.23	0.57	70.1	3.9	74.0	18.5
2nd	13.71	3.53	2.51	0.24	0.28	0.50	71.1	6.9	78.0	14.1

TABLE VIII

	Weight (kilos).	Change of weight during period.	Nitrogen in Food.	Excretion of N in urine (gram.).				Partition of N in urine (per cent.).			
				Urea N.	Ammonia N.	Uric Acid N.	Undeter- mined N.	Urea.	Ammonia.	Uric Acid.	Undeter- mined.
Case 1.	Jan. 23-28	46.15	12.79	6.68	4.09	0.23	0.39	66.9	3.8	6.5	23.8
	Feb. 1-6	46.11	13.75	8.66	3.68	0.24	1.83	72.3	4.7	6.7	16.3
	Feb. 7-12	46.08	15.98	9.32	4.91	0.40	1.01	74.1	6.0	4.8	15.1
	Jan. 23-Feb. 12	—	14.02	8.18	4.14	0.28	1.08	70.9	4.8	6.2	18.1
	Mean.	—	13.42	7.81	4.06	0.17	1.19	72.4	3.0	3.4	21.2
	Feb. 15-21	50.43	—	—	7.08	0.22	1.04	82.4	2.6	2.9	12.1
Case 2.	July 15-21	50.00	13.42	8.59	5.34	0.65	0.70	76.7	9.3	3.9	10.1
	Nov. 25-30	49.30	16.98	10.02	—	—	—	—	—	—	—
	Feb. 1-7	64.46	13.64	8.54	6.43	0.28	1.52	75.3	3.3	3.6	17.8
	Feb. 8-14	64.66	14.38	9.13	6.93	0.37	1.58	75.9	4.1	2.8	17.4
	Feb. 15-21	64.43	14.46	10.61	8.70	0.31	1.39	82.0	2.9	2.0	13.1
	Feb. 1-21	—	14.16	9.43	7.37	0.32	1.30	77.8	3.4	2.6	16.2
Case 3.	June 11-17	62.53	—	13.28	11.51	0.31	1.13	86.7	2.3	2.5	8.5
	Control 1.	69.61	17.04	14.38	12.66	0.67	0.84	88.0	4.7	1.4	5.9
	Control 2.	52.84	—	12.28	10.82	0.23	1.09	88.1	1.9	1.1	8.9
	Control 3.	63.21	15.26	6.69	5.15	0.33	1.09	76.9	4.9	1.8	16.4

stores this in the skin. Now one of their cases of psoriasis was retaining nitrogen at the rate of many grammes daily over a period of four months, and one of the writer's cases of erythrodermia over an even longer period. The calculation given above in this latter case of the weight of the protein and its necessary fluid makes it impossible to believe that a true accumulation of nitrogen can be occurring in the absence of any comparable gain in weight. The amount of protein is considerably more than would be present in a human body. For these reasons it appears that no true accumulation of nitrogen occurs. It must therefore pass from the body by some other path than the urine and faeces.

(2) It has been suggested that some abnormal path of excretion exists apart from the skin. Such an explanation is inherently improbable. Nitrogen has never been detected escaping from the lungs in the form of ammonia or other volatile compound.

(3) The nitrogen is lost through the skin. The obvious method of testing this possibility is to collect the scales shed and estimate their nitrogen content. Schamberg and Kolmer did this in some of their cases of psoriasis. In no instance did the daily content of nitrogen exceed one gramme.

Unfortunately the difficulty of collecting the scales quantitatively is very great. Higher figures have been found in other investigations, which may be mentioned here.

It will be recollected that Schwenkenbecher and Spitta (7) showed that the normal loss of nitrogen was about one-third of a gramme daily.

Burgsdorf (28) collected the scales in a case of exfoliative dermatitis and found that the nitrogen content gave a daily average of 0.82 of a gramme. Quinquaud (29) collected the scales from a case of generalized psoriasis for a month and found that the nitrogen corresponded to 4.24 gm. daily. Von Noorden (30) weighed the scales from a case of psoriasis, the nitrogen content being 3.94 gm. in twenty-four hours.

In order to avoid the loss of serum, Van Noorden kept a patient with pemphigus vegetans continually in a bath for twenty-four hours. The water was found to contain 5 gm. of nitrogen. There is a possibility of error in this method. Selenew (22) in a case of pemphigus foliaceus mentioned above found an average of 5 gm. of nitrogen daily in the scales. He believed that the collection was not complete.

The protein metabolism in this last case may be considered. It is obvious that the nitrogen excreted in the urine and faeces must be daily many grammes less than the nitrogen ingested in the food. Further, in view of the improbability that the collection of scales can be quantitative, the apparent retention of nitrogen would be incompletely accounted for by the nitrogen in the scales. This case therefore theoretically should have shown, and actually did show, the same changes in metabolism that have been found in the researches on psoriasis and erythrodermia which are being considered. On these grounds there can be no doubt that the observed retention of nitrogen in all these varieties of

dermatitis is apparent and not real, and is accounted for by loss from the affected skin.

It is noticeable that the total excretion of nitrogen in the urine falls to extraordinarily low figures. In one of the cases of psoriasis it fell to 1.88 grm. on one day when on a low diet, this being the lowest excretion ever recorded in a human being apart from renal inefficiency. Similar figures occurred in exfoliative dermatitis, although the diet was not restricted. Apparently the products of the metabolism of food are almost entirely excreted by the skin, the urinary nitrogen resulting mainly from the endogenous metabolism.

The Excretion of Uric Acid.

The excretion of uric acid in the cases of exfoliative dermatitis will now be considered. It is generally accepted that various cutaneous conditions are associated with disturbances of the intermediary metabolism. Xanthoma and diabetes may be given as an example. Now many skin diseases have been supposed to have a 'gouty' origin, and amongst these are some forms of erythrodermia. With this point in view the uric acid excretion was estimated throughout.

It will be seen from Table VIII that the excretion in the control cases was within normal limits. These cases were in the same wards and took the same diet as the cases of erythrodermia, and hence there can be nothing in the diet which should cause an increased uric acid excretion. Care was taken throughout to exclude those articles which are known to cause an increased excretion. In the cases of exfoliative dermatitis the uric acid excretion is increased not only relatively to the total nitrogen but also absolutely. Further, this excretion is highest in the earliest periods of the analyses, at which time the eruption was most severe. It appears justifiable to conclude that there is an increased excretion of uric acid which bears a relation to the severity of the eruption. It may be mentioned that the leucocytes did not rise above 8,000 in any of these cases. There was occasional pyrexia in Case 1, rising once to 100° F. In Case 2 it did not exceed 99°, and in Case 3 it was normal.

Clinically the three cases were not quite similar, for the first was a primary erythrodermia, the second a recurrent erythrodermia, while the outbreak in the third was undoubtedly due to the application of oil of cade, which had been used in an ointment. The use of this again subsequently caused a relapse. Since all these cases show an increase in uric acid excretion, that excretion would appear to be the result of the dermatitis and not the cause.

A calculation may be made to show approximately what the excretion of uric acid should be in these patients.

In a normal individual the uric acid excreted is the sum of the endogenous and exogenous uric acid and for a mixed diet is approximately as follows:

- (1) Endogenous uric acid nitrogen = 0.01 gramme per 10 kilos body weight.

(2) Exogenous uric acid nitrogen = 0.01 gramme per gramme of urinary nitrogen. This is 1 per cent. of urinary nitrogen, and is equivalent to about 0.9 per cent. of nitrogen in the food.

This formula for the calculation of the uric acid nitrogen is suggested because it is obvious that in these cases the total nitrogen in the urine bears no relation, or a very abnormal one, to the metabolism of the body or to the diet, and no guide can be obtained from the urinary nitrogen as to what may be called the normal excretion of uric acid. Such a calculation can only give an approximate result, but it agrees closely with the figures published for normal persons on an unrestricted mixed diet.

On this basis the excretion of uric acid nitrogen in Case 1 (Table VIII) for the period Jan. 23 to Feb. 12 should be 0.19 grm. As the observed mean is 0.36 grm., there is an abnormal excretion of 0.17 grm. Apparently this must come from the endogenous metabolism. Now in the deeper layers of the skin, metabolism must be abnormally increased. In a generalized exfoliative dermatitis inflammation, proliferation, and destruction of cells must be proceeding rapidly over a large area. It may be suggested that the increased endogenous uric acid is the direct result of the condition of the skin.

It is noticeable that a high excretion of uric acid is present in Case 3, although the eruption was practically absent at the time of the analyses. It is possible that the condition of the deeper layers of the skin had not yet returned to normal. An analogy may be drawn from diabetes. Glycosuria is the outward expression of hyperglycaemia. After the glycosuria has disappeared hyperglycaemia will still be present for a period. So when the eruption has disappeared, the abnormal condition of the skin which has led to that eruption may still be present. This would also explain the retention of nitrogen persisting after the disappearance of the eruption in psoriasis, if Schamberg and Kolmer's contention is found to be correct. There is no period in the analyses of erythrodermias which gives any assistance on this point. It might be possible to decide these questions by histological examination.

The abnormal condition of the skin may well precede the eruption as well as survive it, and this would explain the low excretion of nitrogen which numerous investigators claim to have found shortly before relapses in certain diseases of the skin and to which we have already referred.

Other nitrogenous constituents of the urine may be briefly mentioned. Ammonia is normally so variable in amount that no deductions can be drawn from its excretion.

There is not sufficient evidence to arrive at any conclusions with regard to creatinin. The undetermined nitrogen is a still more difficult question, since it is calculated by difference, and contains the sum of the experimental errors of all the analyses. In the analyses of exfoliative dermatitis the undetermined nitrogen (which includes creatinin) is within normal limits. Some attention has been directed to amino acids, but in the most recent work by Neiditsch (31) the excretion was found to be within normal limits in a wide range of skin diseases.

Treatment.

There is one suggestion with regard to treatment which may be made. Schamberg and Kolmer found a distinct improvement in the condition of the skin while their patients suffering from psoriasis were on low protein diets, although local treatment had finally to be resorted to in order to obtain a complete cure.

According to the views which have been expressed in this review the skin in these conditions is making use of an abnormal amount of protein. The limitation of protein in such circumstances may be compared to the limitation of carbohydrates in glycosuria.

Certainly it is reasonable that the effect of a low protein diet should be tried in those conditions of the skin which are associated with a diminished excretion of nitrogen.

General Conclusions.

1. Changes in the nitrogenous excretion in various dermatoses are the result of the condition of the skin and are not connected with the cause of the disease.

2. Retention of nitrogen is apparent and not real and is accounted for by the abnormal excretion of nitrogen by the skin.

3. Changes in the nitrogenous excretion may precede the eruption, and it is possible that they also survive it.

4. A low protein diet is worthy of trial in those forms of dermatitis which are associated with disturbances of the nitrogenous excretion.

REFERENCES.

Normal Metabolism.

1. Weintraud, *Berl. klin. Woch.*, 1895, xxxii. 407.
2. Umber, *Zeitschr. f. klin. Med.*, Berlin, 1896, xxix. 174.
3. Folin, *Amer. Journ. Physiol.*, Boston, xiii. 117.
4. Burian u. Schur, *Archiv f. d. ges. Physiol.*, Bonn, 1900, lxxx. 241.
5. *Proc. Physiolog. Soc.*, 1906, xxxiv. 13.
6. Maillard, *Compt. rendus*, Paris, 1908, cxlvii. 710.
7. Schwenkenbecher u. Spitta, *Arch. f. exp. Path. u. Pharmak.*, Leipz., 1906, lvi. 284.
- 7 a. Graham and Poulton, *Quart. Journ. Med.*, Oxford, 1913-14, vii. 13.

Metabolism in Diseases of the Skin.

8. Tenneson et Lyon, *Ann. de Dermat. et Syph.*, Paris, 1888, 2^e sér., ix. 431.
9. Bar et Tissier, *ibid.*, 1895, 3^e sér., vi. 951.
10. Gaucher et Claude, *ibid.*, 1896, 3^e sér., vii. 1064.
11. Wilenski, *Thèse de Paris*, 1895.
12. Perrin, *ibid.*
13. Thilliez, *ibid.*
14. Leredde, *Gazette des Hôpitaux*, Paris, 1898, lxxi. 329; *Ann. de Dermat. et Syph.*, Paris, 1899, 3^e sér., x. 711.

15. Pini, *Giorn. ital. Syph. e del. mal. ven.*, Milano, 1898, xxxiii. 354.
16. Audry Gerard et Dalons, *Ann. de Dermat. et Syph.*, Paris, 1901, 113.
17. Allgeyer, *Dermat. Zeitschr.*, Berlin, iv.
18. Hardouin, *Ann. de Dermat. et Syph.*, Paris, 1900, 1137.
19. Stüve, *Arch. f. Dermat. u. Syph.*, Wien, 1896, xxxvi. 191.
20. Radaeli, *Giorn. ital. Syph. e del. mal. ven.*, Milano, 1901, 416.
21. Radaeli, *ibid.*, 1903, xxxviii. 349.
22. Selenew, *Dermat. Zeitschr.*, Berlin, 1905, xii. 569.
23. Gaucher et Desmoulières, *Journ. de Physiol. et de Path. gén.*, Paris, 1904, vi. 703, and 1905, vii. 316.
24. Brocq, Desgrez et Ayrignac, *V. Internat. Dermat. Kongress*, 1904; *Ann. de Dermat. et Syph.*, Paris, 1905, 681 and 781, and 1906, 433.
25. Johnston and Schwartz, *New York Med. Journ.*, 1909, lxxxix. 535.
26. Schamberg, Ringer, Raiziss, and Kolmer, *Journ. Cutan. Diseases*, New York, 1913, xxxi. 698.
27. Tidy, *Brit. Journ. Dermat.*, London, 1911, xxiii. 133.
28. Burgsdorf, *Berl. klin. Wochenschr.*, 1903, xl. 151.
29. Quinquaud, *Congr. internat. de Dermat.*, Paris, 1890, 729.
30. Von Noorden, *Pathology of Metabolism*, 754.
31. Neiditsch, *Archiv f. Dermat. u. Syph.*, Wien, 1913, cxvi. 31.

Some Analyses also in the following Articles :

- Thibierge, *Ann. de Dermat. et Syph.*, Paris, 1889, 799.
 Hallopeau et Fournier, *ibid.*, 1892, 1163.
 Wickham, *ibid.*, 1893, 1184.
 Jullien, *ibid.*, 1893, 1207.
 Engman (Indican), *Journ. Cutan. Diseases*, 1907, 178.
 Polano, *Dermat. Centralblatt*, 1909, 194.
 Johnston, *Journ. Cutan. Diseases*, New York, 1912, xxx. 136.

Articles of a Theoretical Character.

- Lewin, *Kongr. d. d. Dermat. Gesellschaft*, 1892.
 Waelsch, *Prag. mediz. Wochenschr.*, 1905, xxx. 591, 607 and 637.
 Ullmann, *Wiener med. Presse*, 1905, xlvii. 1125.
 Desgrez et Ayrignac, *Comptes rendus*, Paris, 1904, cxxxix. 900.
 Duncan, Bulkley, and others, *Discussion. V. Internat. Dermat. Kongress*, Berlin, 1904.
 Pollitzer, *Journ. Cutan. Diseases*, New York, 1909, xxvii. 483.
 Brocq, *Ann. de Dermat. et Syph.*, Paris, 1910, 5th ser., i. 156.
 Stelwagon, Fox, and others, *Discussion. Journ. Cutan. Diseases*, New York, 1907, xxv. 157.
 Haslund, *Archiv f. Derm. u. Syph.*, Wien, 1912, cxiv. 427, 745.
 Sibley, *Med. Press and Circular*, Lond., 1913, xc. 547.
 Clark, *New York Med. Journ.*, 1913, xcviii. 511.

General Reviews.

- Jadassohn, *V. Internat. Dermat. Kongress*, 1904, II. Band, II. Teil.
 Block, *Ergebnisse d. inn. Med. u. Kinderheilk.*, Berlin, 1908, ii. 521.
 Von Noorden (Salomon), *Pathology of Metabolism*, 45.

THE TREATMENT OF CONGENITAL SYPHILIS¹

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If anything were necessary to enforce on us the importance of the treatment of this malady, surely the long list of manifestations (recent and late), now believed to be due to the *Spirochaeta pallida*, apart altogether from the great loss of life in the form of abortions and still-births that can be ascribed to it, would be sufficient. And from the fact that these are such frequent occurrences it is amply evident that our methods of the past have been anything but effective. Mercury will undoubtedly alleviate the active symptoms of syphilis, and will even in a certain number of cases cause a positive Wassermann reaction to become negative, and remain so, but all are agreed that a cure can be attained, even with prolonged administration of the drug, only in a few instances. In salvarsan, however, we have a more potent spirochaetocide, a remedy which has been fairly extensively tried in the acquired form of the disease in adults, but less thoroughly in the congenital variety as it affects infants and very young children. That it has not fulfilled its first expectations is no reason why we should decry it, as has unfortunately become only too common of late. And because it acts better when reinforced with mercury does not mean that the drug is impotent. We have seen two cases of condylomata due to congenital syphilis which had resisted treatment with mercury for several months, and in which, nevertheless, two intravenous injections of neosalvarsan caused a rapid cure. Quite recently, too, we had the opportunity of observing a girl of 20 years with severe osteitis of twelve years' duration due to congenital syphilis. For many years her life had been rendered miserable by night-pains, although mercury had been administered off and on all the time, and she was unable to follow any employment. After two intravenous injections of salvarsan the pains completely disappeared, and definite absorption of some of the new-formed bone resulted. The patient could not remember ever being so well as she was after the salvarsan therapy, and is now able to earn her own livelihood. The results that one of us (L. F.) has obtained in the treatment of mental deficiency due to congenital syphilis are further evidence of the efficacy of the remedy.

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Congenital syphilis has always been recognized as a most obstinate form of the infection, and there is no doubt that this fact, and the need to treat it more heroically, and for a more prolonged period, have deterred many from pursuing salvarsan therapy. Moreover, there has always been the fear, expressed first of all by Ehrlich himself, that such a potent germicide would bring about a fatal toxæmia in infants consequent on the death of innumerable spirochaetes and the liberation of their endotoxins. In our opinion, as will be shown later, this danger has probably been overestimated.

In view of the usually accepted belief that it is difficult, indeed almost impossible, to administer the drug to infants and young children intravenously, it has been given intramuscularly, rectally, or through the medium of the mother's milk, but we think that most authorities are agreed that when presented in these two latter ways salvarsan possesses only a very limited power.

In our first attempts with salvarsan the drug was given by intramuscular injections, chiefly because our cases were out-patients, and we considered that this was the safest method under the circumstances. When used in this manner it certainly possesses a high degree of efficiency, but the pain resulting from the injection and the necrosis and sloughing that not infrequently supervene are very serious objections. The pain alone would deter us from ever again giving salvarsan by the subcutaneous or intramuscular routes. An infant with less acute sensations does not appear to suffer so much, but a child of one or two years, or more, simply screams with pain immediately afterwards. A previous injection of cocaine did not seem to diminish the pain to any extent. Within twenty-four to forty-eight hours the seat of injection becomes red, swollen, and tender, so that if given into the buttocks, a not unusual site, the child is unable to sit for many days. Occasionally the inflamed area becomes necrosed and sloughs, leaving an ulcer behind. This course of events has been our experience not only with neosalvarsan, but also with joha, in which the drug is suspended in liquid paraffin. This latter preparation is said by the makers to be non-irritating, and one is advised to select a site for injection free from nerves, most minute directions being given for the selection of a spot near the crest of the ilium. Joha, however, did not seem to be any less irritating than neosalvarsan: there was quite as much pain and swelling after the injection; necrosis followed more frequently, and the remedy in this form was more slowly absorbed.

The efficiency of this route of administration may be judged from Table I giving a synopsis of the clinical histories of cases so treated.

With the exception of pain, induration, and necrosis at the seat of injection, no untoward results occurred in any of our cases. Two of the patients died, but so long afterwards (six months) that the fatal termination cannot be ascribed in any way to the drug. In three of the nine cases, i.e. 33 per cent., the Wassermann reaction was negative fourteen and sixteen months after the last injection, and the children were in good health. Other three of the children were much improved, but the blood test remained positive. One case was lost sight of.

In consequence of the behaviour of the drug when introduced intramuscularly we determined to give it intravenously. As several injections are necessary, and as it is impossible in an infant or young child to employ the veins of the arm, unless when exposed by an incision, we followed the method first described by Noegerrath (1) in 1911. This author selected as the seat of injection the veins of the scalp, which are very prominent in infants, especially in emaciated infants. Any one who has had much practice in performing intravenous injection in the ear of the rabbit will, as a rule, find the operation in babies comparatively simple. It must be admitted, however, that, so far as the prominence of the scalp veins is concerned, children vary considerably, and in some cases, though fortunately very few, it is almost impossible to perform the operation. The chief difficulty is not to enter the vein, but to remain there when once in. The vascular wall is so thin that it is only too easily transfixated, and if the child's head move in the slightest the point of the needle will almost certainly go right through.

Simpson and Thatcher (2) utilized the external jugular vein; but without the aid of an anaesthetic the operation is exceedingly difficult, and in our opinion the employment of an anaesthetic for this purpose is hardly justifiable, especially if the treatment must be frequently repeated. These authors, however, only in very few instances gave a second injection. Owing to the difficulty of keeping a child's head steady sufficiently long to allow many cubic centimetres of fluid flowing into the vein, concentrated solutions of the drug were used. We have now performed many hundreds of injections with concentrated solutions of neosalvarsan, not only though chiefly in children, and we have never seen the slightest harm arise. If the solution be injected very slowly it will be sufficiently diluted by the blood as it flows past the point of the needle. In infants we seldom inject more than 3 or 4 c.c. of saline containing 0.05 to 0.3 gm. of neosalvarsan, and in adults, as a rule, 5 c.c. with as much as 0.6 gm. of the drug. The injections to older children and adults were given into a vein of the arm. On one or two occasions attempts were made to make use of the external jugular vein, but the difficulty of the operation, unless with the aid of an anaesthetic, made us early abandon such a route.

The operation is carried out with strict aseptic precautions. The hair may require to be cut, but in the majority of young infants this is quite unnecessary, and the part can be efficiently cleaned with methylated ether. The all-important point is to avoid any movement of the head. The child is laid on a high couch with the head resting on a pillow and firmly supported by the hands of an assistant, who at the same time causes pressure on the proximal portion of a vein. This, along with the crying of the infant, usually suffices to make the vein stand out prominently. A needle is then inserted into the vein and one judges whether or not one is in the lumen from the free flow of blood. (By this same procedure enough blood can easily be obtained from the youngest infants for the performance of the Wassermann reaction.) When satisfied that the needle is properly within the lumen of the vein, but not unless, the syringe containing the solution of the remedy is fixed in position, and slowly emptied. Should the vein not be

properly entered the fluid will accumulate outside immediately pressure is exerted on the piston, and the same train of symptoms which follow the intramuscular injection will result. Experience has taught us that it is unwise to attempt to readjust the needle in a transfixed vessel, and that it is better to withdraw the needle, select another site, and repeat the process.

We have invariably used a 5 c.c. Record syringe and No. 1 will be found the most suitable size of needle. One might be tempted to select a somewhat finer needle, and for very small veins a No. 15 may be employed, but with the larger size we find that there is less chance of passing through the vein, and sufficient blood for the Wassermann test is more easily obtained.

With practice the operator will become so expert that within the matter of an hour about ten injections can be administered. Not infrequently, on account of thrombosis having taken place, it will be found impossible to enter the same vein, at least at an identical spot, on a later occasion, but there are, as a rule, sufficient veins to enable one to give twelve to twenty successive injections without using the same place twice.

Our experience is entirely limited to neosalvarsan, which we employed partly because it is supposed to be less toxic than old salvarsan, but chiefly on account of the ease with which it dissolves. In all we have administered something like 400 injections of concentrated solutions of the drug, and can only record one fatal issue. To this accident we will refer later. The smallest dose which we have given has been 0.01 gm. per kilo body weight. Frequently the primary dose was 0.02 to 0.03 gm. per kilo, and in a few of the older infants 0.05 gm. per kilo. Our present opinion is that the usually recommended dose of 0.005 gm. per kilo is too small, and in this we are supported by Welde (3), who, after considerable experience, ultimately decided that 0.1 gm. for an infant was a safe amount to administer. We would advise an initial dose of 0.05 gm., i.e. 0.015 gm. per kilo, for newborn infants, gradually increased in successive doses to 0.2 or even 0.3 gm. per injection. As a rule we injected once weekly, but in view of the fact that some of the young infants, who were very severely infected and who died seven or eight days later, had improved for the first five or six days, we think it advisable to repeat the injection within four days.

All our cases were treated as out-patients, and consequently the opportunities for observing reactions were limited. The most frequent reaction we have met with is vomiting. Probably 50 per cent. to 60 per cent. of the injections were followed by vomiting. This might last for several hours, in some cases till the next day or even the day after, but as a rule the child was quite well by the following morning. Some of the children were never upset in the slightest by the treatment, and a child might be sick and vomit on one occasion and not on another. Slight looseness of the motions occasionally accompanied the vomiting. On one occasion three children injected with the same solution immediately afterwards developed rigors and became cyanosed; their temperatures rose to 102° and 103° F. At the time the children looked

very ill, but by evening all had recovered, and one of the little patients when visited at home was found sitting on her father's knee eating kippered herring.

At times the children would increase in weight after the injection, and at other times lose weight, and that quite apart from any gastro-intestinal disturbance. As a rule, the earlier injections, while clearing up the specific manifestations, caused the child to lose weight, the loss being due, in all likelihood, to a poisoning from the liberated endotoxins. This loss of weight on commencing treatment we have also noticed with mercury.

As previously mentioned, our cases were out-patients, and in many instances they were living under the worst possible conditions, so that had we had the opportunity of treating them in a hospital ward better results might have been obtained. Since, however, most of the cases were in this way still able to be suckled, the better hygienic conditions in a hospital might have been counter-balanced by the necessary resort to artificial feeding.

Summary of Results.

1 child died within	12 hours of the injection.
1 " "	3 days after the first injection.
1 " "	4 " " seventh injection.
5 children died	7 to 8 days after an injection.
3 " "	10 " " "
2 " "	14 " " "
3 " "	21 " " "
1 child died	1 year after cessation of treatment.

Five children were living one, one, five, twelve, and twelve months after the last injection, but the mothers refused either to continue the treatment, or to allow of blood being withdrawn for the Wassermann test.

Fifteen children gave a negative Wassermann reaction after cessation of treatment, and in six cases this was still negative six, seven, seven, eight, eleven, and fourteen months after the last injection.

Five children were lost sight of.

As previously mentioned, we can only record one fatal issue from the treatment. This child had been given, one week previously, a dose corresponding to 0.05 grm. per kilo with good results, but succumbed within twelve hours to a second dose of the same amount. The child became comatose and never regained consciousness.

The child who died three days after the injection was a very severe example of the disease, and had received a dose corresponding to 0.01 grm. per kilo.

The case which only survived four days had received in all seven injections, the dosage varying between 0.03 and 0.05 grm. per kilo. As a result of the

treatment the child improved considerably, but developed tubercular cervical adenitis and died quite suddenly—cause unknown.

Of the five children who lived only seven to eight days after an injection four were under seven weeks of age. Two had received a dose of 0.015 gm. per kilo, and had steadily improved until the day before death; one after a dose of 0.016 gm. per kilo improved for five days and then relapsed; one who had received two injections of 0.03 gm. per kilo developed convulsions seven days after the last injection, and one succumbed from acute broncho-pneumonia.

Of the three children who succumbed ten days after the injection one developed intussusception the day after a series of ten injections of a dosage of 0.025 gm. per kilo; peritonitis through the abdominal wound bursting was the cause of death. Each of the other two children had only received two injections of a dosage of 0.025 gm. per kilo body weight.

The two deaths occurring fourteen days after the last injection were both due to broncho-pneumonia. One of the cases had received nine injections, the dosage varying between 0.025 and 0.03 gm. per kilo, and the other seven injections with a dosage of 0.01 to 0.035 gm. per kilo.

Of the three children who died three weeks after an injection one had received eleven injections in doses varying between 0.012 and 0.036 gm. per kilo, and had greatly improved, but developed measles and died three weeks later. One had received three injections of a dosage of 0.05 gm. per kilo, and died from whooping-cough, and the other, also after three injections of a dosage of 0.03 to 0.04 gm., developed convulsions.

The only other death that we have to record occurred from broncho-pneumonia one year after the cessation of treatment.

Most of the deaths, it will be admitted, were in no way associated with the method of treatment, or with what some might be tempted to describe as too large doses of the drug. They were for the most part due to the disease itself, to the results of infections of the respiratory tract, or to the sequelae of some of the specific fevers. Indeed, from the fact that many of the cases were severe and had improved for five to six days after the injection, only to relapse, and also since salvarsan is supposed to be entirely excreted within four days of its introduction, we might have saved some cases that were lost by even more heroic treatment. Of the sixteen children that died within three weeks of an injection nine were under three months of age when treatment was commenced. With mercury and salvarsan our death-rate in cases under three months was 43 per cent., whereas in a series of fourteen cases also under three months, but treated with mercury alone, the death-rate was 71 per cent. (see Table II). A table (No. III) is appended giving details of the cases treated by intravenous injection of salvarsan.

Encouraging as these results are, they leave much to be desired, and stimulated by the work of Jeanselme and Galliot (4) and others, we determined to try antenatal salvarsan treatment, i.e. treatment of the mothers during pregnancy,

since it has been shown by these workers that it is possible by such a procedure to obtain healthy infants in from 86 per cent. to 100 per cent. of the cases.

Antenatal treatment by mercury and iodide of potassium has, of course, often been practised, and can, as we ourselves are in a position to testify, give good results. Only too often, however, in spite of continued treatment, still-births and miscarriages persist, and even should the infant be born alive it not infrequently develops specific manifestations some time later. Galliot quotes the statistics of Pinard, Champetier de Ribes, and Polocki, who, by prolonged treatment with mercury and iodide of potassium, obtained 75.9 per cent. of the children healthy. This high proportion of successful results must no doubt have been due to the thoroughness with which the treatment was carried out, yet it falls short of the 93.3 per cent. obtained by Sauvage with salvarsan, and of Fabre and Bourret's 100 per cent. of healthy children.

During the past six months we have treated seven pregnant women with mercurial inunctions and neosalvarsan intravenously, but as yet only three have been delivered.² In no case has the treatment seemed to interfere with the course of gestation; in fact, except for the headache and sickness, which were frequently troublesome for some twelve hours after the injection, all the patients expressed themselves as feeling very well, and much better than during the previous pregnancy. In no case did albuminuria develop, and the mothers already confined have made rapid and complete recoveries. Concentrated solutions of the drug were always used, as much as 0.6 grm., and in two instances 0.9 grm., being dissolved in 5 or 10 c.c. of saline. The patients who received the 0.9 grm. suffered from severe headache and sickness and vomiting for several days afterwards, and in consequence we decided not to repeat the larger dose. Probably the wiser course would be to administer small doses frequently, say 0.3 grm. weekly, till a definitely negative Wassermann reaction has been obtained. The mercurial inunctions should, however, be continued throughout the whole course of the pregnancy.

The following are summaries of the clinical histories of the three cases which have been delivered :

No. 1. Mrs. M. (mother of No. 36, Table III).

Five pregnancies; no miscarriages.

Fifth child definitely syphilitic.

W. R. strongly positive in mother and child.

21/2/14. Seven months pregnant. Mercurial inunctions commenced.

22/2/14. 0.6 grm. neosalvarsan intravenously.

1/3/14. 0.6 grm.

8/3/14. 0.6 grm.

22/3/14. 0.9 grm. After this injection patient was very ill for several days.

7/4/14. W. R. still positive but weak.

25/4/14. Child born.

² Since this paper was sent to press the other four mothers have been delivered and the children, varying in age between two weeks and four months, appear absolutely healthy.

- 22/6/14. W. R. in child (aged 8 weeks) absolutely negative, and in mother positive but very weak. Child in excellent health.
 10/12/14. Child 7 months old; in very good health; one tooth; there has never been any rash and there is no splenic enlargement.

No. 2. Mrs. W.

Three previous pregnancies.

First, still-born; second, apparently healthy child of $4\frac{1}{2}$ years; third, case of congenital heart with saddle-nose.

W. R. positive in mother and second and third children.

11/2/14. Mercurial inunctions commenced. $5\frac{1}{2}$ months pregnant. 0.6 gm. neosalvarsan intravenously.

25/2/14. 0.6 gm.

11/3/14. 0.6 gm.

9/4/14. W. R. negative.

19/4/14. 0.9 gm. neosalvarsan intravenously.

Patient was usually troubled with headache and vomiting after the injection, but these were specially severe after the last.

19/5/14. W. R. still negative.

24/5/14. Baby born.

13/6/14. W. R. in baby (aged 3 weeks) absolutely negative.

11/7/14. Child still absolutely healthy; sleeps well; 10 lb.

10/12/14. Child still in perfect health. Aged 7 months.

No. 3. Mrs. McC. (mother of No. 35, Table III).

One previous pregnancy; this child was definitely syphilitic, and both mother and child gave positive W. R.

21/1/14. $6\frac{1}{2}$ months pregnant. Mercurial inunction instituted. 0.3 gm. neosalvarsan intravenously.

10/2/14. 0.6 gm.

25/2/14. 0.6 gm.

19/3/14. 0.3 gm.

19/5/14. Baby born.

13/6/14. Baby aged $3\frac{1}{2}$ weeks weighs 7 lb. 14 oz., and is apparently in good health. No evidence of syphilis. W. R. absolutely negative. W. R. in mother (borderland case).

27/6/14. Child continues very well. Weight 9 lb.

11/7/14. Child still well. Weight 10 lb. 12 oz.

7/10/14. Aged 5 months. Still well. Weight 14 lb. 6 oz.

These results of antenatal treatment by salvarsan, though admittedly limited, are exceedingly encouraging and quite in accord with those of Galliot. This author has collected from different sources statistics regarding 145 pregnant women treated with salvarsan alone, and in 91.72 per cent. of the cases healthy children were born. In our cases mercurial inunctions were also practised. Unfortunately the infants are still young, and it is just possible that some of them may later develop symptoms. In all, however, the Wassermann reaction is definitely negative, and it is most unlikely that they harbour living spirochaetes. It would therefore seem not improbable that antenatal salvarsan therapy, if generally practised, would go far to eradicate congenital syphilis and the high infantile mortality that accompanies it.

Conclusions.

1. Salvarsan is superior to mercury in alleviating many of the manifestations of congenital syphilis.

2. Salvarsan should be administered to infants and young children intravenously.

3. It is advisable to use concentrated solutions of the drug and the veins of the scalp as the seat of the operation in order to avoid the necessity of an anaesthetic.

4. Antenatal treatment is more successful with salvarsan than with mercury.

LITERATURE.

1. Noegerrath, *Jahrbuch f. Kinderh.*, 1912, lxxv. 131.
2. Simpson and Thatcher, *Brit. Med. Jour.*, 1913, No. 2745, 534.
3. Welde, *Jahrbuch f. Kinderh.*, 1912, lxxv. 56.
4. Galliot, *Archives des Mal. des Enf.*, 1913, xvi. 892.

TABLE I. *List of Cases treated with Joka and Neosalvarsan by Intramuscular Injections and Mercurial Inunctions.*

No.	Name.	Age.	Sex.	Dose. grm.	No. of Injections.	Total Amount. grm.	Remarks.
1.	Emma B.	14 months	F.	0.1-0.45	6 in 6 weeks	1.45	Child seen first at age of 4 months with typical manifestations of congenital syphilis, and treated from then till age of 14 months with ung. hyd. alone. W. R. still +. No active manifestations when salvarsan commenced. W. R. negative 1 month and 16 months after cessation of injections.
2.	Lizzie J.	6 years	F.	0.2-0.5	7 in 9½ weeks	2.15	Severe osteitis of both fibulae and right humerus. Interstitial keratitis. W. R. +. W. R. negative 14 months after last injection, but luetin test positive.
3.	Willie B.	4½ years	M.	0.1-0.3	4 in 5 weeks	0.8	Eczema oris. W. R. +. Condition healed with treatment and W. R. became negative. Seen again 10 months later with return of eczema when W. R. was strongly +.
4.	Martha T.	6 years	F.	0.1-0.45	5 in 4½ weeks	1.25	Eczema oris and ophthalmia tarsi. W. R. +. W. R. became negative after 4 injections and was still negative 14 months later.
5.	James McI.	3 years	M.	0.1-0.3	4 in 4 weeks	0.7	Seen with rickets and typical specific macular eruption. Not walking. W. R. +. Older sister with interstitial keratitis also gave a + W. R. With injections patient rapidly improved and after 4 was attempting to walk. Lost sight of afterwards.
6.	John M.	10 years	M.	0.3-0.5	5 in 4 weeks	2.1	Eczema oris. W. R. +. Mouth completely healed with treatment. Seen 14 months later when eczema had returned and W. R. was still + but weak.
7.	Thomas L.	9 months	M.	0.15-0.4	7 in 6 weeks	1.75	Seen at age of 2 months with typical specific manifestations. W. R. +. Treated with ung. hyd. with great improvement. Recrudescence 7 months later owing to intermission of treatment. Neosalvarsan administered intramuscularly with rapid improvement. Child died 6 months after cessation of salvarsan treatment from broncho-pneumonia.
8.	Ellen B.	4 months	F.	0.1-0.2	8 in 10 weeks	1.0	Typical case of congenital syphilis at age of 2 months. W. R. +. Treated with ung. hyd. till age of 4 months. Improved greatly with neosalvarsan intramuscularly. Died 6 months later from broncho-pneumonia complicating whooping-cough.
9.	Walter G.	8½ years	M.	0.3-0.45	5 in 5 weeks	1.9	Extreme mental deficiency—quite unable to read although had been at school for 3 years. Did not play with the other children. W. R. +. Improved with treatment; commenced to learn at school; 1 year after commencement of treatment could read simple sentences, go messages, and was playing with other children. W. R. ? + 6 months after cessation of treatment.

TABLE II. Cases of Congenital Syphilis treated with Mercurial Inunctions of Child, and in Breast-fed Children the administration of KI and Hyd. Perchlor. to the Mother.

No.	Name.	Sex.	Age.	Feeding.	Remarks.	
1.	Thomas B.	M.	10 days	Breast	Severe case of congenital syphilis with extensive implication of lips. No enlargement of spleen. Died 3 days after being first seen.	D.
2.	Robert G.	M.	13 "	"	Severe case of congenital syphilis with pemphigoid eruption. Died 2 days later.	D.
3.	Conrad R.	M.	3 weeks	"	Moderately severe case of congenital syphilis with enlarged spleen and orchitis. negative 1 year later.	W. R.
4.	Eliz. H.	F.	7 "	"	Developed at 5 weeks snuffles, hacking of lips, and typical pigmented scaly specific eruption which implicated face, arms, and legs. Very much enlarged spleen. W. R. + in mother.	W.
5.	David D.	M.	5 " (brother of No. 9)	"	Mother had been treated with KI and Hg since birth of No. 9, i. e. 2 years. Had stillbirth since. At 4 weeks typical specific eruption appeared on buttocks and scrotum, with scaling of palms and dry glazed lips. No enlargement of spleen. Developed convulsions at 11 weeks and died.	W.
6.	Christina C.	F.	6 weeks	"	Moderately severe case with enlarged spleen. Died 3 days later.	D.
7.	Eliz. R.	F.	6 "	"	Severe cutaneous manifestations with slightly enlarged spleen. Seen 18 months later apparently in good health.	D.
8.	M. M.	M.	6 "	"	Severe case with enlarged spleen and haemorrhagic rhinitis. Died next day.	W.
9.	D.	M.	7 "	Bottle	Severe case of congenital syphilis with snuffles and rash of 5 weeks' duration. With hyd. cum cret. little improvement. Rapid improvement with ung. hyd. Died from enteritis at 5½ months. (Brother of No. 5.)	D.
10.	C. McL.	F.	8 "	—	Severe case. Died 2 or 3 days later.	D.
11.	John McG.	M.	8 "	Breast	Severe case with snuffles, extensive cutaneous eruption, and enlargement of spleen. Did not improve much and died within 10 days of broncho-pneumonia.	D.
12.	Daniel McG.	M.	8 "	"	Extensive cutaneous eruption, snuffles, and hacking of lips of 3 weeks' duration. Spleen slightly enlarged.	W.
13.	Eliz. S.	F.	9 "	"	Severe case with jaundice and enlarged liver. Also enlarged spleen. Died 1 month later.	W.
14.	J. R.	M.	9 "	"	P. M. cirrhosis of liver and pyaemia.	D.
15.	Ruby T.	F.	12 "	Bottle	Moderately severe case in which manifestations developed at 1 week. Died 1 month later.	D.
16.	Peter B.	M.	12 "	Breast	Severe case with enlarged spleen. Taking convulsions. Meningitis? Died.	D.
17.	Annie S.	F.	12 "	"	Mild case of congenital syphilis with slightly enlarged spleen. Only treated for 1 month with ung. hyd. Seen 1 year later in apparent good health.	W.
18.	A. C.	F.	15 "	"	Mild case with snuffles and cutaneous eruption on face of 2 weeks' duration. With ung. hyd. condition rapidly improved. Child seen 2 months later when apparently quite well. All treatment had been stopped.	W.
					Moderately severe cutaneous manifestations and enlarged spleen. Died few days later.	D.

TABLE III.

No.	Name.	Sex.	Age.	Dose.	No. of Injections.	Total Amount.	Feeding.	Remarks.
				grm.		grm.		
1.	John F.	M.	11 days	0.1	1	0.1	Breast	Severe case of congenital syphilis with pemphigoid eruption on abdomen and feet; muc. memb. of lips much hacked. Seen 3 and 7 days afterwards when seemed to be improving and all rash had gone. Died 8 days after injection.
2.	Marg. R.	F.	12 "	0.05-0.15	6 in 5 weeks	0.65	"	Seen with syphilitic osteitis of lower end of right humerus—no other manifestations. Child made uninterrupted recovery—6 weeks after commencement of treatment X-rays showed bone normal. W. R. negative.
3.	Eliz. W.	F.	4 weeks	0.025	1	0.025	Bottle	Severe syphilitic cutaneous manifestations. Spleen palpable. Died 3 days after injection. Only weighed 5 lbs.
4.	D. F.	M.	5 "	0.025	1	0.025	Breast	3 previous children stillborn. Very severe cutaneous and mucous membrane manifestations. Seen 7 days after injection and seemed much improved. Died 8 days after injection.
5.	Marg. C.	F.	5 "	0.05-0.2	5 in 6 weeks	0.55	Bottle	Severe case of congenital syphilis with extensive cutaneous eruption, snuffles, hacking of lips, and enlarged spleen. W. R. + in mother. Child steadily improved and was never sick after the injections. Lost sight of after last injection.
6.	Eliz. S.	F.	6 "	0.075-0.2	8 in 7 weeks	1.35	Breast	Seen with very extensive and severe cutaneous syphilitic manifestations. W. R. +. Rapid and marked improvement with treatment. W. R. negative 8 months after last injection.
7.	Mary McG.	F.	6 "	0.05	1	0.05	"	Case of congenital syphilis with hacking of lips, eruption on face and limbs, peeling of palms and soles, and enlargement of spleen. Mother gave + W. R. Child improved with treatment but was soon lost sight of. Was found alive and well 5 months later.
8.	Joseph T.	M.	7 "	0.05	1	0.05	"	Severe cutaneous syphilitic manifestations. W. R. +. Developed broncho-pneumonia and died 1 week later.
9.	Marion K.	F.	7 "	0.1	1	0.1	Bottle	Severe case of congenital syphilis with scaly eruption on thighs, feet and arms, and greatly enlarged spleen—no snuffles nor affection of lips. On 23/6/13 received 0.1 gm. neosalvarsan intravenously and was put on Hg—showed great improvement. Seen again 4/9/13 with bronchitis. Developed pneumonia New Year, 1914—recovered, but died from pneumonia April, 1914.

TABLE III (continued).

No.	Name.	Sex.	Age.	Dose. grm.	No. of Injections.	Total Amount. grm.	Feeding.	Remarks.
10	Wm. C.	M.	7 weeks	0.05-0.15	9 in 10 weeks	1.05	Bottle	Mild case of congenital syphilis—no splenic enlargement. W. R. still + after series of injections. Died 2 weeks after last injection from broncho-pneumonia.
11.	Helen K.	F.	7 "	0.075	1	0.075	—	Severe case of congenital syphilis with cutaneous and visceral manifestations. Improved for 5 days, then got worse and died 7 days after injection.
12.	Jas. M.	M.	8 "	0.1-0.2	5 in 4 weeks	0.85	Breast	Severe case of congenital syphilis with epiphysitis. Rash had entirely disappeared 1 week after first injection. Child rapidly improved but was lost sight of after fifth injection.
13.	Marg. M.	F.	8 "	0.1	1	0.1	"	Seen with laryngitis, snuffles, enlarged spleen, hacking of lips, and cutaneous eruption. W. R. +. Child improved very much with 0.1 grm. Seen 1 month later when child quite well, but lost sight of afterwards.
14.	Mary K.	F.	9 "	0.1-0.2	7 in 6½ weeks	0.95	Bottle	Mild case of congenital syphilis—no enlargement of spleen. W. R. positive in mother. Child greatly improved. W. R. negative 1 week after last injection.
15.	Nancy G.	F.	11 "	0.1-0.25	6 in 5 weeks	1.1	Breast	Seen with syphilitic osteitis at age of 6 weeks, and at 11 weeks cutaneous manifestations developed. Great improvement with salvarsan treatment. Osteitis had been treated with ung. hyd. at first with no manifest change. With salvarsan osteitis rapidly disappeared and child was discharged well. Fourteen months later W. R. negative.
16.	Alice C.	F.	1 "	0.1-0.2	2 in 1 week	0.3	"	Case of congenital syphilis with cutaneous manifestations, snuffles, and hacking of lips of 1 week's duration. Spleen palpable. Mother KI and hyd. perchlor., child ung. hyd. and salvarsan. Within week of first injection rash had all gone, lips were healing, and spleen could not be felt. Child developed oedema of feet and legs 1 week after second injection. This disappeared, but child died few days later.
17.	Sam. S.	M.	3 months	0.1	2 in 1 week	0.2	"	Mild case when seen and was treated for 1 month with mercury alone. Developed convulsions 7 days after last injection and died.
18.	Joe G.	M.	3 "	0.1-0.2	8 in 6½ weeks	1.4	"	Seen with very severe manifestations of congenital syphilis. W. R. was still + after 5 injections. Seen 1 year after cessation of treatment; was very well, but mother refused permission to have blood withdrawn for Wassermann test.

TABLE III (continued).

No.	Name.	Sex.	Age.	Dose.	No. of Injections.	Total Amount.	Feeding.	Remarks.
19.	And. R.	M.	3 months	grm. 0.05-0.2	7 in 7 weeks	grm. 1.05	Breast	Developed syphilitic manifestations at 2 weeks—treated with ung. hyd. At time of salvarsan treatment had orchitis and W. R. +. Improved very much with treatment. After last injection developed bronchitis, which passed into bronchopneumonia with death 14 days later.
20.	Eliz. B.	F.	3 "	0.2	2 in 7 days	0.4	"	Emaciated child with snuffles from birth. One week before being brought for treatment muc. memb. of lips became cracked and a scaly eruption appeared on buttocks. Spleen palpable. Ung. hyd. prescribed for child and pot. iod. and hyd. perchlor. for mother. On 2/6/13 received 0.2 grm. neo-salvarsan intravenously and was not in the least upset. Seen 1 week later when much improved and 0.2 grm. neo-salvarsan again administered. Child became drowsy afterwards and died early next morning. Never really came out of sleep.
21.	Isa S.	F.	3 "	0.1-0.15	7 in 12 weeks	0.95	"	Seen at age of 6 weeks with very severe syphilitic manifestations and treated till age of 3 months with ung. hyd. Received first 7 intramuscular injections of neo-salvarsan in doses varying between 0.1 and 0.15 grm., in all 0.75 grm., but although child improved W. R. +. Then received 2 intravenous injections of 0.1 and 0.15 grm. and W. R. became negative and was still negative 11 months later.
22.	Jas. H.	M.	3 "	0.1-0.3	14 in 16 weeks	2.6	Bottle	Seen with very extensive and severe cutaneous manifestations of C. S. No enlargement of spleen. W. R. +. After 7 injections W. R. still +, after 9 injections weak +, and after 14 definitely negative. Child was greatly improved by treatment.
23.	Jas. McN.	M.	13 weeks	0.05-0.25	11 in 10 weeks	1.4	"	Typical and severe case of C. S.—spleen not enlarged. Developed measles 1 week after last injection and died 3 weeks later. Before measles had improved very much.
24.	Jas. S.	M.	3½ months	0.15	1	0.15	Breast	Moderately severe case of syphilis with snuffles and hacking of lips and cutaneous eruption on face and limbs. No splenic enlargement. Improved very much. Seen 1 month later when apparently well. Mother refused to continue treatment.
25.	Alex. E.	M.	4 "	0.1-0.3	11 in 12 weeks	2.7	—	Seen with snuffles, excoriation of muc. memb. of lips, osteitis of both femora and right humerus causing pseudo-paralysis of limbs. W. R. +. Rapid improvement with treatment. W. R. weak + after 7 injections, negative after 11 injections.

TABLE III (continued).

No.	Name.	Sex.	Age.	Dose.	No. of Injections.	Total Amount.	Feeding.	Remarks.
26.	Dorothy I.	F.	4 months	0.1-0.2 grm	3 in 4 weeks	0.5 grm.	Breast	Mother had been seen 1 year previously suffering from nocturnal headaches which rapidly improved with pot. iod. and hyd. perchlor. Snuffles appeared at age of 3 weeks, with cutaneous rash and enlargement of spleen. With salvarsan and ung. hyd. child rapidly improved. Mother was treated at same time with pot. iod. and hyd. perchlor. Mother ceased to attend after 1 month—child seen 1 year later and seemed absolutely well.
27.	Henry M.	M.	4½ "	0.15-0.2	7 in 6 weeks	1.2	Bottle	Developed snuffles, cutaneous rash, and hacking of lips at 6 weeks. Seen with severe manifestations and syphilitic dacrylitis. Spleen slightly enlarged. W. R. +. Child rapidly improved. At end of salvarsan treatment W. R. negative.
28.	Jas. M.	M.	4½ "	0.1-0.25	11 in 10 weeks	1.95	"	Seen with very severe cutaneous manifestations of C. S.—no splenic enlargement. W. R. +. Greatly improved with treatment. W. R. still + after 7 injections. W. R. negative 7 months after cessation of injections—no ung. hyd. having been used for 2 months previous to withdrawal of blood.
29.	Mary P.	F.	5 "	0.25-0.3	7 in 3 months	1.65	—	Seen with rhinitis, saddle-nose, osteitis of lower end of right radius, and enlargement of spleen. W. R. +. Great improvement with treatment. W. R. negative after cessation of injections.
30.	Robert W.	M.	5 "	0.1-0.3	12 in 8 weeks and 3 in 2 weeks)	2.25	—	Typical case of C. S. No enlargement of spleen. W. R. +. Great improvement with treatment. After 9 injections spread over 8 weeks developed measles. W. R. still +. 2 months later another series of 3 injections given. W. R. became negative. Child greatly improved.
31.	May G.	F.	6 "	0.1-0.3	9 in 12 weeks	1.75	Bottle	Child at 2 months had typical manifestations of C. S. Treated with ung. hyd. alone till age of 6 months. Great improvement with salvarsan. W. R. negative.
32.	Jessie L.	F.	7 "	0.25-0.3	3 in 3 weeks	0.8	—	Case of congenital syphilis with rhinitis, eruption on face, and hacking of lips. W. R. + in mother. Child at first improved but developed whooping-cough and died 3 weeks after last injection.
33.	Jas. G.	M.	7 "	0.2-0.3	3 in 2 weeks	0.7	—	Emaciated child (12 lb. 10 oz.) with rhinitis, saddle-nose, natiform cranium. Died at night. W. R. +. With salvarsan child at first improved and in 3 weeks increased in weight 1 lb.—then lost ½ lb. after last injection and died 3 weeks later.

TABLE III (continued).

No.	Name.	Sex.	Age.	Dose.	No. of Injections.	Total Amount.	Feeding.	Remarks.
34.	Wm. P.	M.	8 months	grm. 0.1-0.3	10 (7 in 15 weeks and 3 in 3 weeks)	grm. 1.85	—	Typical C. S.—no enlargement of spleen. W. R. still + after injections. Child developed intussusception day after last injection and died 10 days later from peritonitis. Child had improved greatly in general health.
35.	John McC.	M.	8½ "	0.15	2 in 3 weeks	0.3	Bottle	Badly developed child with occasional vomiting. Enlarged spleen, saddle-nose. Gave history of typical C. S. at 3 months. W. R. +. Child much better after first injection, but as mother could not look after it properly it was admitted to hospital, where it died some time after.
36.	Alex. M.	M.	9 "	0.2-0.3	7 in 9½ weeks	1.75	—	Severe rhinitis with bronchitis, saddle-nose, enlarged spleen. Developed enlarged cervical glands (? tubercular); died suddenly when apparently quite well 4 days after last injection.
37.	Thos. J.	M.	11 "	0.1-0.3	7 in 6 weeks	1.3	—	Hydrocephalus. Typical history of C. S. shortly after birth. W. R. +. W. R. negative 7 months after last injection (no hyd. for 2 months). Child greatly improved.
38.	Lizzie H.	F.	1½ years	0.15-0.2	5 in 6 weeks	0.95	—	Case of spastic diplegia. No history of injury at birth. W. R. + in mother and child. Treated with ung. hyd. and neo-salvarsan. Improved, but lost sight of after last injection.
39.	Wm. M.	M.	1½ "	0.1-0.15	4	0.55	—	Seen with anal condylomata. Resisted treatment with mercury alone. Condylomata had entirely disappeared after fourth injection.
40.	Annie B.	F.	2 "	0.1-0.3	12 in all (5 in 4 weeks and 7 in 8 weeks)	2.75	—	Seen with rickets, saddle-nose, and enlarged spleen. W. R. +. After first 5 injections W. R. still +. Child much better and beginning to walk. 6 months later got another series of injections of 0.2 and 0.3 grm.—7 injections in all. Child still better, walking quite well. W. R. negative.
41.	Janet R.	F.	2 "	0.2-0.3	6 in 8½ weeks	1.45	—	Seen with severe rhinitis, saddle-nose, anal condyloma. W. R. +. Had suffered from snuffles and cutaneous manifestations at 1 month. With salvarsan treatment condyloma quickly disappeared but rhinitis more slowly. Six months later child in good health; rhinitis quite better, but nose had fallen in greatly. W. R. definitely negative.
42.	Pat. McA.	M.	12 "	0.25-0.4	7 in 6 weeks	2.55	—	Seen with extensive syphilitic osteitis of both tibiae and left femur. Child greatly improved. W. R. 1 month later, negative.
43.	John S.	M.	3 months	0.1-0.2	4 in 4 weeks	0.75	—	Plump child with pigmented squamo-bullous eruption on buttocks, soles of feet, and round the mouth of 1 week's duration. No enlargement of spleen. W. R. in mother +. Rash rapidly disappeared. Child only sick once after one of the injections. Lost sight of. Very well on day of last injection.

TWO CASES OF PATENCY OF THE DUCTUS ARTERIOSUS

By T. WARDROP GRIFFITH

THE two examples of patency of the ductus arteriosus on which I desire to comment occurred in patients in whom the affection was recognized during life. One of these succumbed to infective endocarditis, and the diagnosis was verified on the post-mortem table. In the other the condition was probably associated with some further anomaly of the great vessels and with a developmental error which had given rise to cyanosis, for this is a symptom which is not often met with in uncomplicated cases of patency of the arterial duct.

CASE I.

The first patient, a young unmarried woman of 32, very anaemic, somewhat wasted and short of breath, was sent to see me by Dr. Eley of Batley. From her earliest childhood she had been short of breath and she had been unable to join in the more energetic games of her fellows. Her mother volunteered the statement that she had always had a large heart, as she had noticed it beating with undue violence when she was a baby. This had also been noticed by the brothers of the little girl, who, being a few years older, had had the duty imposed upon them of carrying her about.

After examining the patient I wrote to Dr. Eley as follows: 'I think there are really two conditions, a congenital malformation—and here I incline to patency of the ductus arteriosus—and an acquired disease of the mitral valve with both stenosis and regurgitation.'

On March 10, 1903, a few days after I had seen the patient at my rooms, she was, at the request of Dr. Eley, admitted under my care into the General Infirmary at Leeds. The diagnosis of mitral disease was confirmed; a crescendo presystolic bruit at the apex followed by a systolic bruit made the matter clear. Further examination led me to suspect the presence of aortic disease, and as the days passed I became convinced of this. The temperature, which was not quite steady when she was admitted, began to show marked oscillations, and it became increasingly obvious that we had to do with a case of infective endocarditis complicating an old cardiac lesion. There was marked pyorrhoea alveolaris.

The presence of a systolic and diastolic bruit due to aortic disease introduced an element of difficulty into the diagnosis of the condition of patent ductus arteriosus. This was made on the following grounds. At the inner end of the second left intercostal space there was heard a loud systolic bruit, followed by a very loud diastolic bruit which was audible a considerable distance outwards along the second space and was not transmitted along the left edge of the sternum. I was particularly struck by the continuity of the two bruits; the

only way in which they could be regarded as separated from one another was by the occurrence of the greatly accentuated second sound which was heard with its maximum at the inner end of the second space. As I repeatedly pointed out to my class of students, there were not two bruits, but one continuous bruit with systolic and diastolic increments, and so striking was this that I frequently said the sound was not adequately described as 'to and fro' but rather as 'to and to'. It gave me the impression of a sound caused by the passage of fluid in a continuous stream, in the same direction, but with varying degrees of force. The systolic and diastolic increments were, I thought, most striking at the beginning of these periods; certainly this was the case in respect of the diastolic increment. No one has described this physical sign better than the late Dr. G. A. Gibson (1), who wrote as follows: 'Beginning distinctly after the first sound, it accompanies the latter part of that sound, occupies the short pause, accompanies the second sound, which may be accentuated in the pulmonary area, or may be and often is doubled, and finally dies away during the long pause.'

When this physical sign has been definitely established, a diagnosis of patency of the ductus arteriosus or of some other kind of communication between the aorta and pulmonary artery may safely be made. The alternatives I considered were the following:

1. That the signs were altogether due to disease of the pulmonary segments. Against this was the fact that, though there was marked venous pulsation in the neck, there was no great dilatation of the right side of the heart; the second sound of the heart in the pulmonary area was loud, and there was no cyanosis. The rarity of disease of the pulmonary valves of a kind likely to produce signs resembling those met with perhaps influenced me against this diagnosis, though, as we had reason to believe the patient was the subject of infective endocarditis, a well-known cause of disease of the pulmonary segments was present. In this connexion I was not unmindful of a case I had put on record in 1906 in which infective endocarditis was confined to the pulmonary valve (2).

2. That the signs were altogether due to disease of the aortic segments. Now there was no doubt that disease of the aortic valve was present, and the signs of regurgitation became increasingly obvious. Direct and regurgitant bruits were heard in the usual situation and the pulse was of the Corrigan character. It is true that the bruits of aortic disease are sometimes heard better to the left of the sternum than to the right, but in this case the excess in loudness at the inner end of the second left space was so great as to demand some other explanation.

These considerations, coupled with the remarkable continuity of the systolic and diastolic parts of the bruit, led me to diagnose patency of the ductus arteriosus.

Very distinct pulsation could be seen and felt towards the inner end of the second and third left interspaces. Dr. Rowden, who is in charge of the radiographic department of the Infirmary, was good enough to make an examination of the patient in my presence with the fluoroscopic screen. This revealed the presence of a pulsating area in the situation of the stem of the pulmonary artery, as though that vessel were greatly dilated.

The assistance which may be obtained by the use of the orthodiagraph in the diagnosis of patency of the ductus arteriosus has been well emphasized by Wessler and Bass (3). With their permission I reproduce one of the diagrams in their paper, in which the dilatation of the pulmonary artery under the unwonted strain of the aortic pressure acting through the patent ductus is well seen (Fig. 1).

3. There remained of course a third alternative diagnosis, namely a communication between the aorta and pulmonary artery due to an aneurism of one or the other. The age and sex of the patient made this very unlikely. In

connexion with endocarditis of the infective variety it is well known that aneurisms of the stem of the pulmonary artery or of the aorta may arise, and that communications may in this way be caused. In this case, however, there was every reason to think that the infective endocarditis was of recent origin, and that some abnormal condition of the heart associated with enlargement had been present from earliest childhood and probably from birth.

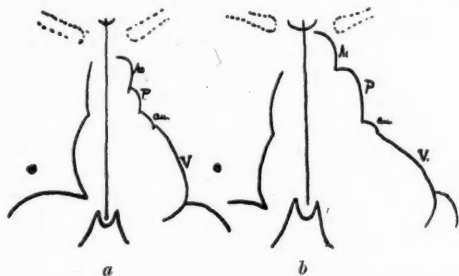


FIG. 1. After Wessler and Bass. (a) Orthodiagram; normal condition; (b) Enlarged (and pulsating) pulmonary artery (P).



FIG. 2. Shows the mitral stenosis; infective mitral and aortic valvulitis and the bilobed aneurysmal dilatation of the pulmonary artery.



FIG. 3. Shows the mass of vegetations in the pulmonary artery; a probe is passed along the patent ductus arteriosus.

The patient remained under my observation till her death on July 27, 1913. It is not relevant to my subject to comment on the treatment which was followed. At one time the intensity of the infective process seemed to be lessening, but during the last few weeks of her life the patient got steadily weaker and it was clear that the end was imminent. She died rather suddenly after an attack of urgent dyspnoea.

During the last few weeks of her life we were struck by the complete disappearance of the characteristic continuous bruit which I have described and on which I had relied in the diagnosis of the condition.

At the autopsy, which was made by Dr. Matthew J. Stewart, there was

found considerable enlargement of the heart, which weighed about $14\frac{1}{2}$ oz. There was marked hypertrophy without notable dilatation of the right ventricle. There was recent pericarditis, and before the heart was removed there was found on the anterior and left aspect of the pulmonary artery, which was generally dilated, a large bilobed aneurysmal swelling, which is well seen in Fig. 2. There was old-standing disease of the mitral valve with moderate stenosis of the orifice, and both this valve and the aortic segments presented large fungating masses of vegetations. Evidence of recent endocarditis was found at the junction of the two posterior segments of the pulmonary valve (Fig. 3). The lumen of the pulmonary artery was almost occluded by a large mass of blood-stained vegetations, which was gently adherent to the walls of the vessel at two situations. One of these was at the anterior and left aspect of the artery, where there was a double concavity corresponding to the convexity seen from the outside; the other was around the opening of the ductus arteriosus, and into this there projected a conical mass of vegetations so as completely to occlude the aperture. When the ductus was cleared of this it permitted the passage of a No. 9 catheter. The space left for the passage of the blood between the mass of vegetations and the wall of the vessel was probably much greater during life than one might expect from an inspection in the post-mortem room, where the dilating influence of the blood-pressure would be absent.

The diagnosis of patent ductus arteriosus was therefore confirmed and the disappearance of the characteristic sign of the continuous bruit accounted for by the occlusion of the aperture.

It must be remembered that while the function of the ductus arteriosus during foetal life is to convey the greater part of the blood which leaves the right ventricle into the descending part of the aorta, its patency after the establishment of the ordinary circulation will be attended with a flow in the opposite direction, namely from the aorta to the pulmonary artery, and that this will be the case both during the systole and during the diastole of the heart. The pulmonary artery will therefore be subjected to the pressure of the powerful left ventricle and will be liable to undergo dilatation. Then we must remember that those who are the subjects of congenital malformations of the heart are peculiarly liable to endocarditis both of the simple and of the malignant variety. In making an analysis of some sixty cases of malignant endocarditis of the pulmonary valve Dr. Newton Pitt (4) found patency of the interventricular septum in ten cases, congenital pulmonary stenosis in eight, and patency of the ductus arteriosus in three. Should this complication occur, and especially, as in this case, should the wall of the artery be profoundly affected, the occurrence of great aneurysmal dilatation may be readily understood.

In this connexion I may refer to a case put on record by the late James Foulis (5) in 1884. From the figure which is reproduced from his paper (Fig. 4) it will be seen that there is aneurysmal dilatation of the left and anterior wall of the pulmonary artery with extensive infective pulmonary valvulitis and endarteritis. Foulis states that on the wall of the aorta opposite to the opening of the ductus into that vessel there was a bulging, one inch by half an inch in extent, partly filled with coagulum. He is clearly of opinion that the systolic part of the bruit which was heard was due to the passage of blood from the pulmonary artery to the aorta, and that the diastolic part was due to blood

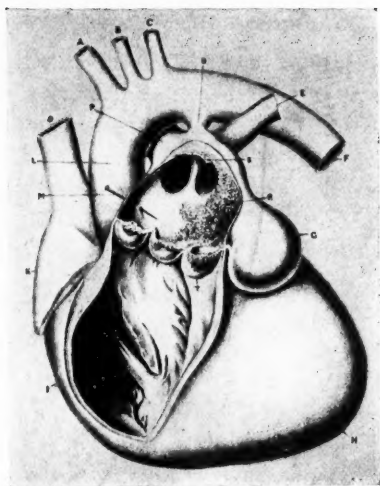
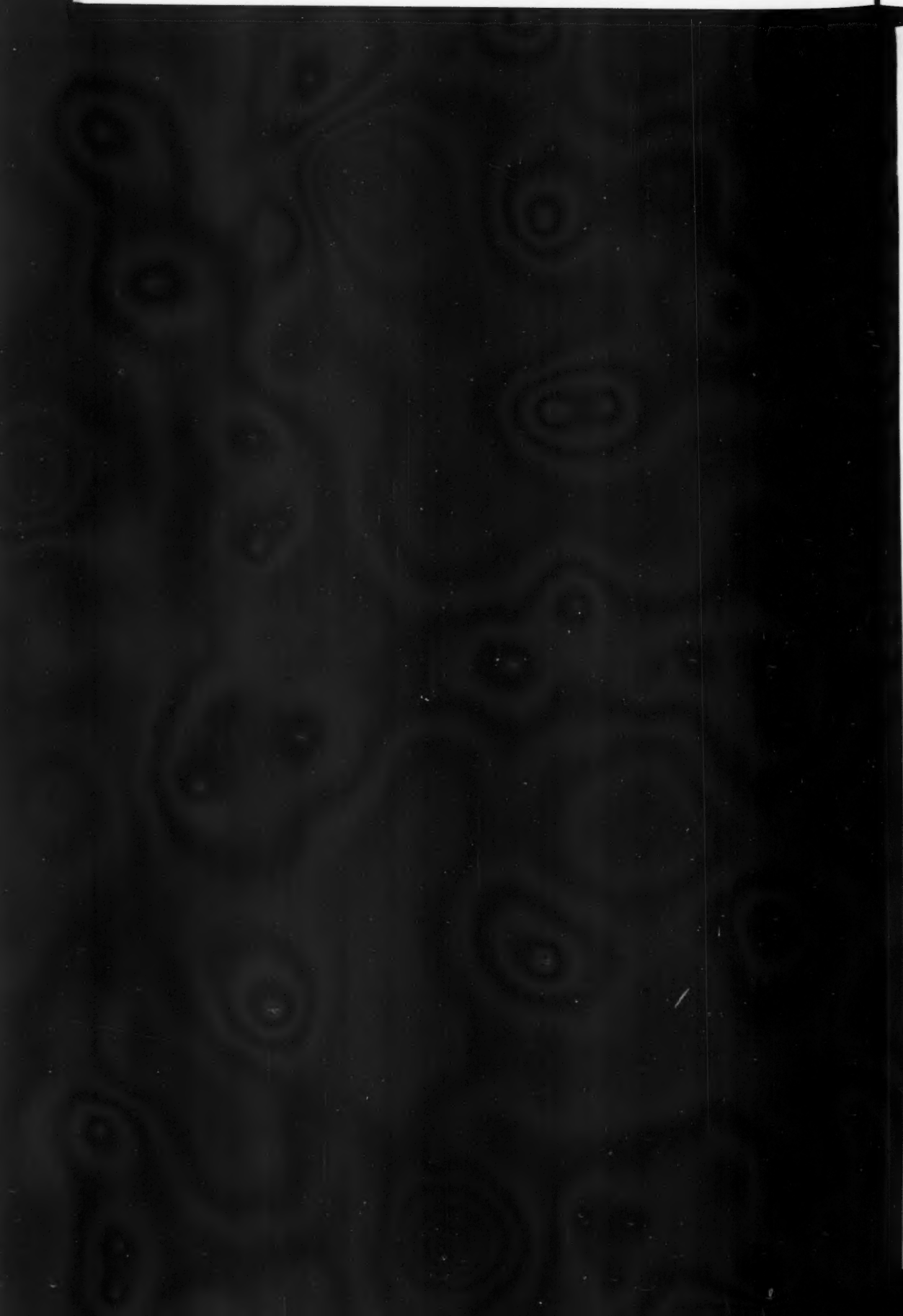


FIG. 4. From the paper by Foulis.



flowing in the opposite direction. As he points out, the long axis of the patent ductus would, if prolonged in either direction, impinge on the pulmonary artery and aorta at the parts where these vessels are diseased. Yet it is hard to understand how blood can be driven from the pulmonary artery into the aorta, in which one must suppose the blood-pressure to be higher; and it is especially difficult to admit this in the case recorded by Foulis, for it is stated that the right ventricle was thin-walled and that the wall of the left ventricle was thickened. If it is the case that sometimes the right ventricle bursts open the pulmonary valve before the left ventricle has overcome the aortic pressure, we might understand a very transient flow from pulmonary artery to aorta; apart from this it is hard to see how it could occur as the result of simple patency.

Those who have many opportunities of making autopsies in cases of congenital malformations of the heart, especially when the symptom of cyanosis has been present, meet with many examples of patency of the ductus arteriosus. Perhaps the commonest cause of this is the condition usually spoken of as

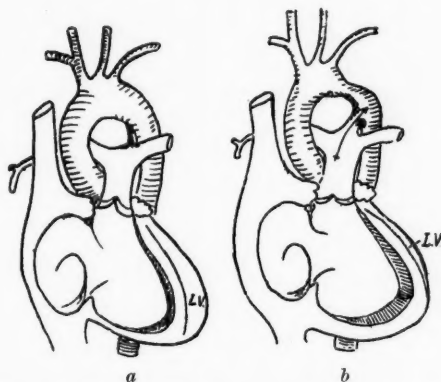


FIG. 5. (a) Normal condition; (b) Coarctation of aorta; LV = left ventricle.

congenital 'pulmonary stenosis'. Arthur Keith (6) has shown us that this is indeed seldom due to an inflammatory process affecting the valves, but to an imperfect development of the bulbus cordis. The result of it is that the blood-pressure in the pulmonary artery is so low in consequence of the lessened flow from the right side of the heart that the ductus cannot close, there being a continuous flow from the aorta to the pulmonary artery, and in this way the lungs get their blood supply.

In the interesting condition known as coarctation of the aorta, if there be much constriction of the vessel, the ductus may remain patent, and may be the means of transmitting blood from the pulmonary artery to the aorta, in which the blood-pressure will at this point be low.

In these two conditions the cause of the patency of the ductus arteriosus is readily explicable. Where there is no other developmental anomaly it is not so easy to understand. Imperfect expansion of the lungs during the earlier part of

extra-uterine life might be invoked as an explanation, and the higher blood-pressure in the aorta than in the pulmonary artery would tend to perpetuate the condition.

It will be interesting to consider the effect that these anomalies may exercise on the mechanism of the circulation. In the normal condition (Fig. 5, *a*), where the foetal passages are closed, it is clear that the same amount of blood will leave the left ventricle by the aorta as enters the right auricle by its venous orifices. In respect of the various functions of the four chambers of the heart we find the size of the cavity and the thickness of the wall of each to be that which we regard as normal.

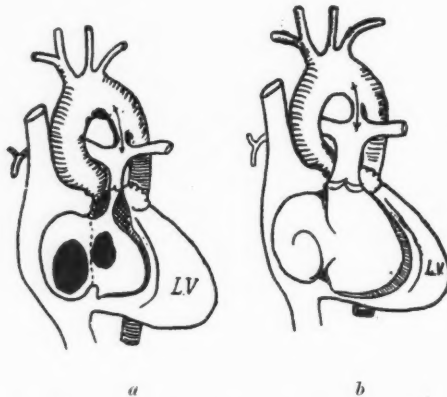


FIG. 6. (*a*) So-called pulmonary stenosis; (*b*) Simple patency of ductus arteriosus.

In coarctation of the aorta (Fig. 5, *b*) with a marked degree of constriction we should expect to find some diminution in the size and thickness of the left ventricle and of the first part of the aorta. The right side of the heart, on the other hand, will have to deal with a larger amount of blood and will have the additional work imposed upon it of maintaining a considerable part of the systemic circulation, and so it will undergo dilatation and hypertrophy.

In arrest of development of the bulbus cordis, with 'pulmonary stenosis' (Fig. 6, *a*), there will usually be wide patency of the foramen ovale or of the interventricular aperture or of both. In consequence of this the right ventricle will dwindle in size and in thickness, and there will be dilatation and hypertrophy of the left ventricle, as it will have to accommodate a greater amount of blood and will have to maintain the greater part of the pulmonary as well as the systemic circulation.

When there is a patent ductus arteriosus without other anomaly (Fig. 6, *b*), and where, as is probable, the flow of blood is always from the aorta to the pulmonary artery, there will I think be less blood circulating in that part of the system beginning in the aorta at the opening from this of the ductus,

and ending at the opening of the inferior vena cava into the right auricle. In respect of this the right auricle will have less blood to deal with, and so consequently will the right ventricle and the trunk of the pulmonary artery. In consequence of the patency of the ductus arteriosus there will be an augmented flow of blood along the branches of the pulmonary artery, and this will prevail through the left side of the heart till we again reach the critical point where the ductus leads off from the aorta. In the outline diagrams I have made I have tried to give expression to the changes in the size and thickness of wall of the various cavities of the heart under these various conditions.

I have said that there is not usually any cyanosis in cases of uncomplicated patency of the ductus arteriosus. Some of the blood will indeed pass twice through the lungs before going to the general system, a condition just the converse of that which prevails in cases of arrested development of the bulbus cordis with consequent patent ductus. On the other hand, the right ventricle will have some extra work imposed on it; though it may be dealing with a smaller amount of blood it has to drive that into a system in which the pressure is higher than normal. If it fails to do so satisfactorily there may result some stagnation of venous flow and some measure of cyanosis.

CASE II.

The second patient came under my observation when he was a boy of five years of age. He had never been strong, had always had some measure of bronchitis, and was suffering from some dyspnoea. There was some cyanosis and the veins of the face, neck, chest, and abdomen were all slightly prominent. The heart was enlarged. On July 27, 1906, I dictated the following note to the clinical clerk in charge of the case: 'There is a systolic bruit which is louder in the aortic and pulmonary areas than at the apex. This is not louder in the pulmonary than in the aortic area. Behind it is high pitched and seems to last beyond the systole. In the episternal notch there is a thrill with its acme in the systole but not disappearing altogether during the diastole. There is no enlargement of the liver. The fingers and toes are slightly clubbed at their extremities.' As the clinical clerk had written that there was a systolic bruit audible with its maximum at the apex I can read into the above note an effort to correct his observation and perhaps some surprise that the bruit was not louder in the pulmonary area than in the aortic. I diagnosed congenital malformation of the heart, and stated that 'pulmonary stenosis' was the common condition found when there was cyanosis, but further than this I did not at that time go. The patient was again admitted under my care on April 18, 1914. There was slight cyanosis, but the lad was sharp and cheerful though rather undersized for his age, which was 13. There was no enlargement of the liver. The cardiac impulse was diffuse and was felt and seen one inch to the right of the sternum and one inch outside the left nipple line. It also extended further up than normal. The inner end of the left clavicle was seen to present a systolic elevation with each beat of the heart. There was well-marked venous pulsation in the neck. No thrill could be made out anywhere. A diastolic thud was palpable to the left of the middle of the sternum. On auscultation the second sound was most marked at the inner end of the first

interspace of the right side. At the apex the first sound was doubled. As the stethoscope was carried from the apex upwards and inwards, a faint bruit was found to lead off from the second sound when the left margin of the sternum was reached; this rapidly increased as the instrument was carried upwards and to the right, and when the inner end of the first right space was reached there was found to be a continuous humming sound with systolic and diastolic increments. These sounds were all heard at their maximum at this point, but they could be heard a considerable distance outwards along the first right interspace. At the back of the chest the continuous hum could be heard on both sides of the spine, but it was louder on the right side than on the left. It could be heard as far down as the sixth dorsal spine, but its maximum was at the fourth. The bruit I have mentioned had very much the same characters as that in the case I have already detailed. It was quite continuous and conformed in all respects except in situation to Gibson's classical description.

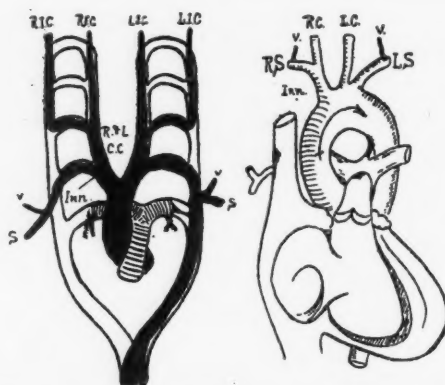


FIG. 7. To show the development of the normal condition with the left aortic arch. (In the schema of this figure the permanent systemic vessels are shown by the thick black shading, the pulmonary vessels by cross marking, and the fibrous remains of the ductus arteriosus by a thin black line.)

It did not appear to me that any valvular lesion could account for the bruit met with in this case. There appeared to be two conditions only which could account for the sounds heard, and these were some communication between the aorta and the superior vena cava or a patent ductus arteriosus. A continuous humming sound, with systolic and, it might be, diastolic exacerbations, might well be heard in this situation if there were an aperture of communication between the aorta and the superior vena cava. In a young lad it would, on the one hand, be hard to suggest a cause for such a condition, and, on the other hand, if such a communication did exist we should expect marked distension and tortuosity of the veins of the neck and chest, for the thin-walled superior vena cava and its tributaries are ill adapted to resist the pressure generated by the contraction of the left ventricle.

If the alternative view of patency of the ductus arteriosus is entertained, we are met with the difficulty that the signs are on the right side and not on the left. The normal development of the great vessels is shown in Fig. 7, where it is seen that the ductus arteriosus is derived from the distal part of the fifth

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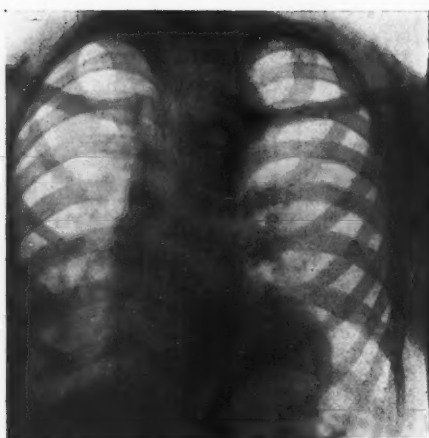


FIG. 9. Shows the extension of the supracardiac shadow to the right, and the well-defined extension upwards and to the left under the clavicle.

left branchial arch. A condition of complete transposition of the viscera would account for the abnormal area in which the sound was heard, but the apex beat was palpable to the left of the sternum and the liver dullness was on the right side, so we had to exclude *situs inversus*.

Sometimes, however, transposition of the arch of the aorta without transposition of the heart is met with, and most anatomical museums are able to show one or more specimens of this anomaly. The development of this condition is shown in Fig. 8. The first part of the aorta has its usual relation to the pulmonary artery, being at first behind it and then to the right-hand side. From this the aorta arches over the root of the right lung instead of the left, and passes to the back of the chest on the right of the spine. When this is the case the ductus arteriosus may be developed on one side or on the other. If it is

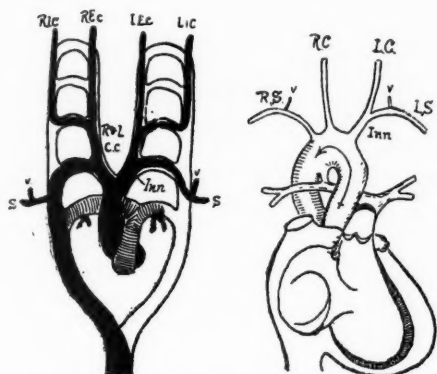


FIG. 8. To show the development of a right aortic arch without transposition of the heart, ductus (right-sided) being patent.

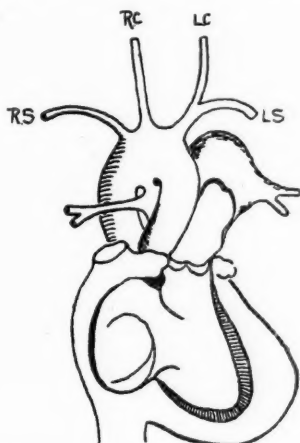


FIG. 10. To show the condition believed to be present; a right arch, without transposition of the heart; ductus arteriosus developed on the right side and remaining patent; greatly dilated pulmonary artery.

developed from the distal part of the fifth right branchial arch, the humming bruit with its systolic and diastolic exacerbations would be heard as it was in the case under discussion, on the right side rather than on the left.

Dr. Rowden made an examination with the radiographic screen and came to the conclusion that there was a distinct widening of the supracardiac area of opacity referable to the great vessels. This extended further to the right than usual and the appearance of its right margin was suggestive of an aortic origin. A well-marked extension of the opaque area passed upwards and to the left, and presented very distinct pulsation. It was clearly this which caused the systolic elevation of the inner end of the clavicle. The skiagram (Fig. 9) shows some of these points, but not so well as the fluoroscopic screen.

After a full consideration of the findings by the various means of investi-

gation I incline to think the condition may be that which I have represented in Fig. 10, in which there is transposition of the arch of the aorta without transposition of the heart, and in which the ductus arteriosus has been developed, and has remained patent, on right side. It is assumed that there is great dilatation of the pulmonary artery and that this is accountable for the pulsating shadow extending up towards the left clavicle.

It may be that the cyanosis has its explanation in the difficulty which the right ventricle experiences in discharging its blood into the pulmonary artery, seeing that this is being fed from the aorta by the patent ductus. On the other hand, there may be some further cardiac anomaly. I have, however, seen too many cases of the morbus coeruleus, and made too many autopsies for the investigation of the underlying conditions, to venture on any definite suggestions as to what that further anomaly may be.

REFERENCES.

1. *Edinb. Med. Journ.*, 1900, N. S., viii. 212.
2. *Lancet*, Lond., 1906, ii. 973.
3. *Amer. Journ. Med. Sci.*, 1913, N. S., cxlv. 543.
4. Allbutt and Rolleston, *System of Medicine*, 2nd ed., 1909, vi. 310.
5. *Edinb. Med. Journ.*, 1884, xxx. 17.
6. 'Malformations of the Bulbus Cordis', *Aberdeen University Quatercentenary Publications*.

ALTERATIONS IN ARTERIAL STRUCTURE, AND THEIR RELATION TO SYPHILIS¹

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INTRODUCTION.

BEFORE classifying the chief abnormalities in the structure of arteries it is necessary to give a brief description of the normal structure, including the alterations which are associated with growth under normal conditions.

Normal Structure.

The arteries have three coats—the tunicae intima, media, and adventitia. According to the structure of the media, or middle coat, the arteries can be divided into ‘*elastic*’ and ‘*muscular*’ arteries. In both varieties the media is composed of involuntary muscle, fibrous interstitial tissue, and elastic; the muscle fibres are, with few exceptions, arranged circularly. In the media of the elastic arteries the elastic fibres are very abundant, stout, and arranged in lamellae; they form the most conspicuous constituent of the coat. In the media of the muscular arteries the elastic fibres are scanty, delicate, and arranged irregularly; they form an insignificant component of the coat in comparison with the muscular fibres. The pulmonary artery and its branches, the aorta, innominate, sub-clavian, common carotid, and part of the internal and external carotid arteries

¹ Being lectures which the writer was prevented by illness from delivering in the Special Syphilology Course given by the London Hospital in February and March, 1914. Statistics have been added. The lectures contain a summary of views expressed in lectures delivered for the London University in May, 1913, ‘On the physiological and pathological changes in the structure of arteries, and on arteriosclerosis’.

[Q. J. M., April, 1915.]

are elastic arteries. These arteries, with the exception of the pulmonary arteries, pass into muscular arteries; the transition is remarkably abrupt.

The media of both types of artery is bounded internally by a sheet of elastic known as the boundary *lamella* (*membrana elastica limitans interna*). In all the arteries, with the exception of the smallest, a second layer of elastic can be distinguished in the intima, lying internal to the elastic lamella. This layer consists of longitudinally directed fibres; in transverse sections of arteries, when stained by Weigert's elastin, it is much blacker than the lamella. It is called the boundary *stripe*.

The *adventitia* of the majority of the muscular arteries consists of a well-developed layer of stout collagenous and elastic fibres, which are for the most part arranged longitudinally. The zone of elastic fibres constitutes the *membrana elastica limitans externa*. The cerebral arteries are exceptional in that the adventitia contains only one or two very delicate elastic fibrils, arranged circularly. The adventitia is poorly developed in the elastic arteries.

In some muscular arteries—for instance, the coronary arteries near their origin—a special layer consisting of longitudinally directed muscle fibres forms the outer part of the media; in the larger branches of the artery this muscular layer narrows and is incorporated within the adventitia; in the smaller branches it is not present.

Changes in the Arteries during Growth of the Individual.

The coats of the arteries increase in size during the growth of the body. In the case of the intima this increase is associated with the development of layers of special structure. The development of the intima is most constant and most conspicuous in the *aorta*. First a layer of longitudinally directed muscular and elastic fibres, the '*musculo-elastic layer*' of Thoma (1), develops between the lamella and the stripe. Then, internal to the stripe appears a layer which is composed of tiers of circularly directed elastic and muscle fibres; the elastic fibres are the most prominent constituent. This layer is the '*hyperplastic layer*' of Jores (2). Both layers increase in breadth, but ultimately the hyperplastic is broader than the musculo-elastic. The innermost portion of the hyperplastic layer may in late life be almost entirely fibrous; this fibrosis is the result of degeneration (*vide* page 209). The extent of the development of the intima varies in different portions of the *aorta* and is not constant in individuals of the same age.

It is impossible, therefore, to give more than approximate dates for the development of the intimal layers. A musculo-elastic layer is present in the thoracic *aorta* at birth and appears in the abdominal *aorta* within two or three months after birth. The hyperplastic layer is usually well developed at the age of ten years; it appears first in the thoracic *aorta* and may appear as early as the third year. At, and after, twenty-five the hyperplastic layer usually exceeds the musculo-elastic in thickness.

In the *other large elastic arteries* similar musculo-elastic and hyperplastic layers are developed, but in these arteries the extent of the development of the layers exhibits more focal variation than in the aorta.

In the *muscular arteries* a development of the intima similar to that in the elastic arteries takes place, but under normal conditions it is much more focal and of less magnitude.

The separation of the musculo-elastic and hyperplastic layers in the intima by the elastic stripe, given in the above descriptions, is not constant. Frequently the musculo-elastic layer is developed not only between the elastic lamella and stripe, but also on the inner aspect of the stripe. This is especially frequent in the muscular arteries, and in the developments of abnormal magnitude which indicate hypertrophy.

Functions of Media and Intima.

The functions of the media, and of the musculo-elastic and hyperplastic layers of the intima, must be indicated to some extent by their anatomical structure. The contraction of the circular fibres of the media, under the influence of the nervous system, narrows the lumen, and also increases the resistance to expansion. The hyperplastic layer of the intima, doubtless, reinforces the media. The longitudinal muscle fibres in the musculo-elastic layer of the intima, and in the special medial and adventitial layers of some arteries, by their contraction react against longitudinal extension of the artery by the pulse wave. The question whether the muscular coats of the media and intima merely govern the size of the lumen and passively resist distension and extension must be decided by physiologists. The remarkable hypertrophies to which the coats are liable suggest that the involuntary muscle plays a more active part in the propulsion of the blood, and behaves in a manner more akin to that of the involuntary muscle in other tubes. I suggest that the involuntary muscle of the arteries not only governs the size of the lumen and offers resistance to expansion and extension, but also contracts in response to the mechanical stimulation of the pulse, the character of the reaction depending upon the condition of tonus.

Classification of Abnormalities in Structure.

The chief abnormalities which affect the arteries may be divided into: I. Hypertrophies; II. Degenerations; III. Infiltrations; and IV. Inflammations.

The *hypertrophies* may be defined as developments which are abnormal in magnitude, but normal in histological structure.

Degeneration and necrosis occur as passive elements of inflammatory reactions, but the characteristic of inflammation is an active reaction. The term *inflammation* should, therefore, be confined to reactions which are essentially active.

Degeneration and necrosis can also occur, either unaccompanied by any active reaction, or only associated with an active reaction which is excited secondarily by the irritation of their products. Such processes, in which degeneration and necrosis are the primary and essential lesions, may be distinguished as *degenerations*.

Many processes of *infiltration* in the arteries are so intimately associated with degeneration and necrosis that an attempt to treat infiltrations independently would only lead to confusion. For simplicity, however, it is advisable to treat separately 'amyloid infiltration'.

PART I.

HYPERTROPHIES.

1. *Medial Hypertrophy.*

Hypertrophy of the media of the muscular arteries is constantly associated with persistent elevation of the blood-pressure. I have obtained some evidence that a certain degree of hypertrophy of the media of the elastic arteries is also associated with heightening of the blood-pressure, but my investigation is not yet concluded; the technical difficulties of the research are great.

Hypertrophy of the media of the muscular arteries is the essential element in the form of arteriosclerosis which is found when the systemic blood-pressure is abnormally high, whether the high blood-pressure is associated with renal disease, or is not. To the condition of high blood-pressure unaccompanied by renal disease the name 'hyperpiesis' has been given by Clifford Allbutt (3). In cases of persistent high blood-pressure in the systemic circulation the hypertrophy of the media is accompanied by a hypertrophy of the heart, in which the left ventricle is disproportionately increased. The degree of hypertrophy in the heart and the arteries is so closely related that it is possible to form an approximate estimation of the increase in the weight of the heart from microscopic examination of the arteries, for instance of the arcuate and interlobular arteries of the kidneys. The hypertrophy of the media of the arteries, like the hypertrophy of the myocardium, is an expression not of degeneration but of physiological activity. The blood-pressure is not raised by the increased force of the hypertrophied heart alone; the active contraction of the hypertrophied arteries is a factor of equal, or greater, importance.

This condition of *cardiovascular hypertrophy*, which is the anatomical indication of an abnormally high blood-pressure, may be present in persons who have been infected by syphilis. If infection by syphilis induces, directly or indirectly, the condition, then the incidence of the condition should be greater in syphilitics than non-syphilitics. I have examined our records of necropsies

for the years 1912 and 1913 in order to ascertain whether there is evidence of this.

In these two years there were 107 necropsies in which lesions of acquired syphilis² were present. The youngest subject was 27, the oldest 81. Cardiovascular hypertrophy was present in 13, that is in 12.03 per cent.

Between the ages of 27 and 81 there were 815 subjects without syphilitic lesions. Cardiovascular hypertrophy was present in 93, that is 11.4 per cent.

According to these figures the incidence of cardiovascular hypertrophy is slightly greater in subjects showing syphilitic lesions.

Of the 107 syphilitic subjects, however, only one, a man aged 81, was over the age of 72. It would, therefore, be fairer to compare the syphilitics and non-syphilitics between the ages of 27 and 72.

Between these ages there were 106 syphilitics, and cardiovascular hypertrophy was present in 12, i. e. 11.3 per cent. There were 787 non-syphilitics, and cardiovascular hypertrophy was present in 90, i. e. 11.4 per cent.

The proportion of cases in which cardiovascular hypertrophy was associated with nephritis to the cases of hyperpiesis was almost identical in the syphilitics and non-syphilitics.

The figures obtained for each individual year showed a remarkable similarity.

² In the statistics quoted in these lectures the old differentiation of syphilitic cases into 'congenital' and 'acquired' is retained. Apart from the fact that these terms do not describe the differentiation which they are employed to denote, namely that in one case the infection is acquired before birth and in the other after birth, there are serious objections to their use. Infection during the process of birth, or after birth (for instance, through the mother's milk), may have occurred in so-called congenital syphilis in infants. A more serious objection is that it is impossible to determine by anatomical investigation whether lesions are the result of ante-natal or post-natal infection. The lesions in syphilitic infants under nine months or one year of age are essentially similar to those found in the dead syphilitic foetus; but even in these early months the lesions in older infants show a tendency to present the characteristics of those in adults. In older children, the lesions show only slight, if any, differences from the lesions in adults. Manifestations of so-called 'congenital' syphilis in adults are identical with those of 'acquired'. The differences in distribution and character of the syphilitic inflammatory reaction appear to depend upon the age of the patient at the time of reaction, and not upon ante-natal or post-natal incidence of infection.

Inasmuch as the lesions in infants are very distinctive, and resemble closely those of undoubted ante-natal infection, there is no objection to placing them in a separate group, regardless of whether the infection occurred before, at, or shortly after birth. The infants are doubtless infected in any case by the parents. In older children and adults the differentiation of 'ante-natal' from 'post-natal' infection depends entirely upon clinical history. This is obviously unsatisfactory. Histories are unreliable, and in the majority of cases in a General Hospital no history can be obtained.

It is advisable, therefore, to state here the cases of syphilis in 1908 to 1913 which were differentiated as 'congenital'.

Infants, under 9 months, showing lesions resembling ante-natal infection, 10 cases.

Children and young adults, 4 cases.

Namely: 1. 1908, M., 2 $\frac{1}{2}$. Syphiloma of larynx. Mother contracted syphilis in 1903.

2. 1910, M., 18. Tabes dorsalis. Charcot's hip. Scars over great trochanter and left knee. Wassermann reaction, in serum, positive.

3. 1910, F., 18. Aortitis. 'Paper' scars on left knee and leg. Necropsy on father showed similar aortitis.

4. 1910, M., 10. Scarred palate. Old interstitial keratitis. Scar over lower third of left femur.

The analysis of the cases in 1912 and 1913 does not afford evidence that the incidence of cardiovascular hypertrophy is greater in syphilitics. In the analysis, however, only such persons as showed syphilitic lesions were counted as syphilitics; doubtless among the non-syphilitics there were patients who had been infected by syphilis but showed no lesions at necropsy. Figures obtained by a scientific examination of patients during life would be of much greater value. A physician of wide experience has told me that his clinical practice has convinced him that the incidence of high blood-pressure is greater in syphilitics. Granting, however, that it is true that the incidence is greater in syphilitics, this does not prove that syphilis is a direct or indirect cause. Nothing definite is known concerning the causation of persistently high blood-pressure beyond the observations that certain cases follow nephritis, and that in other cases persons who have taken all that their life offered of toil and pleasure are most commonly affected. If persistent high blood-pressure, particularly hyperpiesis, is more prevalent among syphilitics, the association may merely be due to a greater liability to infection amongst those who have lived 'not wisely but too well'.

Medial hypertrophy is also found in the muscular arteries when the blood-pressure is raised in a particular area, for instance in the arteries of a collateral circulation. I have obtained some evidence that medial hypertrophy also occurs in the elastic arteries when the blood-pressure is raised locally, for instance in the pulmonary arteries when there is resistance to the passage of blood through the lungs.

2. *Intimal Hypertrophy.*

Intimal hypertrophy at any particular period of life is demonstrated by an excessive development of the intimal layers in places in which they are usually found, or by the appearance of these layers where they are not developed under normal conditions. In the hypertrophy either the musculo-elastic or the hyperplastic layer may take the greater share.

In cases of general high blood-pressure intimal hypertrophy occurs in addition to medial. The intimal hypertrophy is very great in the elastic arteries of the systemic circulation. It is also found in varying grade in the muscular arteries. When the general pressure is very high it is extremely conspicuous in the arcuate and interlobular arteries of the kidneys. In spite of George Johnson's writings in 1852 (4) pure hypertrophy of the intima in these arteries is still frequently referred to as a degeneration. Johnson described, correctly, hypertrophy of both the media and the musculo-elastic layer; he called the latter a part of the media.

Intimal hypertrophy is also found in focal high blood-pressure; it is very conspicuous in the pulmonary arteries in cases of resistance to the flow of blood into the left heart, for instance in mitral stenosis.

Hypertrophy of the intima frequently occurs independently of high blood-

pressure. In these cases there is almost invariably definite histological evidence of degeneration of the media. The hypertrophy of the intima here is doubtless a compensatory hypertrophy.

Evidence that a compensatory intimal hypertrophy does sometimes occur over areas of media which have been weakened by syphilitic inflammation will be given below in the description of syphilis of the elastic arteries (Part IV, p. 223).

PART II.

DEGENERATIONS.

A. Degenerations of the Intima.

1. *Atheroma* is a degeneration which affects, and is almost confined to, the intima. It is found in both the elastic and the muscular arteries, but is commoner in the large elastic. The degeneration is characterized by the accumulation of debris, which is at first fatty and is later frequently impregnated by calcium. The Greek word *ἀθήρωμα*, which is derived from *ἀθήρη* or *ἀθήρη*, 'groats or meal, a porridge thereof', and was used by Galen to signify 'a tumour full of gruel-like material' (Liddell and Scott, 1890 (5)), thus defines the condition precisely. In its slightest degree atheroma presents to the naked eye minute yellow 'flecks' and 'powder streaks'. When these are examined microscopically they are found to correspond to areas of intima in which many of the cells are expanded by fat, whilst masses of fat are formed by the disintegration of such cells; minute granules of fat also surround the elastic fibres. In its advanced degree it forms conspicuous 'plaques' and 'buttons'. In these the microscope reveals a mass of fatty and possibly calcareous debris, containing large, fusiform, margarine crystals; these crystals are dissolved during the process of embedding in paraffin and leave 'crystal spaces'; the mass is covered by a layer of fibrous tissue of varying thickness. Slight atheroma is frequently found with the microscope, when it is not visible to the naked eye.

Atheromatous plaques may ulcerate; this occurs most frequently in the abdominal aorta. The ulceration may allow the blood to dissect up the arterial coats. Thrombi may be deposited upon the surface of atheromatous ulcers. This occurs in the aorta when, in cases of lingering death, the blood stream has been slow. Atheromatous areas may cause great narrowing of the lumen of vessels; a small thrombus may complete the occlusion. This is the most dangerous effect of atheroma *per se*. It occurs frequently in the coronary arteries, and is much the commonest cause of fibrosis of the myocardium. The anterior interventricular branch of the left coronary artery is affected most frequently.

The intima is always thickened, to a greater or less degree, where atheroma

is present. This thickening is due to one or more of the following causes: (1) The expansion of the cells when loaded with fat, (2) the formation of fibrous tissue in response to the irritation which is caused by the accumulated products of degeneration, (3) the special liability of areas of hypertrophied intima to undergo atheromatous degeneration. That areas of hypertrophied intima are more liable to this degeneration than areas which are not hypertrophied is clearly demonstrated in microscopic sections of arteries in which there are focal areas of intimal hypertrophy and atheroma is not widely distributed, for instance arteries of children in whom slight atheroma complicates cardiovascular hypertrophy. It is also frequently demonstrated to the naked eye, when scattered powdery dots of fatty degeneration are seen to be confined to longitudinal ridges of intimal thickening. This liability of areas of hypertrophied intima to be affected by atheroma has misled many writers to consider hypertrophy an essential of atheroma, and even to confuse pure hypertrophy with atheroma.

Causes of Atheroma.

It is universally recognized that with advancing age the liability to this degeneration increases. Atheroma has also been caused experimentally by bacterial toxins (Saltikow, 1908 (6)), and investigation of the arteries of children and young people gives evidence that the condition may be caused by various infections. Finally, there is a close relation between atheroma and heightening of the blood-pressure.

It is most important to recognize the *nature of the relation between atheroma and general or local heightening of the blood-pressure*. The nature of the relation is most clearly demonstrated in local heightening of the blood-pressure; for instance, in the pulmonary arteries when there is resistance to the flow of blood in the lesser circulation, or in the systemic arteries in areas of collateral circulation. In such cases the cause of the heightened blood-pressure is obvious, and the atheroma is clearly an effect and not the cause. In general persistent heightening of the blood-pressure the nature of the relation is less obvious, and the atheroma has frequently been regarded as the cause. It has been said that the blood-pressure is raised because the degeneration has caused a loss of elasticity in the arterial wall.

Observations in the post-mortem room supply strong evidence against this assumption. Atheroma is certainly relatively more extensive and more advanced in the arteries of subjects who have suffered from persistently high blood-pressure. Severe atheroma, however, may be associated with atrophy of the heart and of the media of the arteries. Conversely, very high blood-pressure and great cardiovascular hypertrophy may be associated with very little atheroma; this is most clearly demonstrated in the rare cases of persistently high blood-pressure in young children. The degree of cardiovascular hypertrophy at any age varies directly with the average height of the blood-pressure as ascertained during life. The amount of atheroma, other things being equal,

also varies according to the height of the blood-pressure at any particular age; but it is more intimately correlated with the age of the patient. The older the subject the greater is the amount of atheroma, when the degrees of cardiovascular hypertrophy are identical. The amount of atheroma also increases with the length of time during which the high blood-pressure has existed. These observations demonstrate that atheroma in cases of general, as of local, heightening of the blood-pressure is the result and not the cause of the increased pressure.

In cases of persistent elevation of the blood-pressure in the systemic circulation many of the vasa afferentia of the kidneys may be the seat of a fatty degeneration of the intima, an atheroma, which leads to partial or complete occlusion of the lumen. Arterioles in this condition are figured by Gaskell (7). The heightening of the blood-pressure has been ascribed to the resistance offered by these occluded arterioles. The evidence that this atheroma is a result is much stronger than the evidence that it is a cause of the elevation of the blood-pressure. Thus, the patches of atheroma which are frequently found in the hypertrophied intima of adjacent interlobular arteries are obviously secondary degenerations.

Atheroma is, therefore, caused by toxins; it tends to occur in arteries in which the blood-pressure is abnormally high; it also tends to occur in hypertrophied areas of intima whether the blood-pressure is abnormally high or not; advancing age is a factor in its production. The causes of atheroma are probably essentially similar to those of fatty degeneration in other tissues. This is obviously the case when atheroma is caused by toxins. Degeneration in foci of intimal hypertrophy, when the blood-pressure is normal, is doubtless similar in causation to the degeneration which occurs when there is an increase of the blood-pressure. In both cases the hypertrophy indicates that the work to be performed by the intima is abnormally great. The degeneration is not, however, necessarily the result of mechanical injury by strain; it is more probably due to interference with nutrition. The increase in liability to atheroma which accompanies advance in years, whether the blood-pressure is abnormally high or not, is doubtless due to a decrease in vitality which age entails. Such a decrease in vitality occurs in other tissues and is especially conspicuous in sites of regeneration or hypertrophy.

Inasmuch as atheroma may be caused by the toxins of bacterial infection, it might be expected to be a complication of syphilis. I have not, however, been able to find evidence in the post-mortem room that syphilis induces atheroma, except in that the intima over areas of syphilitic inflammation of the elastic arteries is liable ultimately to fatty degeneration and calcification (Part IV, p. 224). The very slight amount of disseminated atheroma in the aorta of the majority of syphilitics is, indeed, a great assistance in recognizing the inflammatory syphilitic basis of focal areas of intimal thickening.

2. *Intimal fibrosis.* This is merely a modification of atheroma. The muscular and the elastic fibres gradually disappear and the intima becomes occupied by a dense fibrous tissue. Fatty degeneration occurs in the course of

the degeneration and necrosis, but the fatty degeneration is not massive; it does not give rise to atheromatous debris. The course of this gradual degeneration can be followed in the intima of the abdominal aorta in old subjects.

B. Degenerations of the Media.

1. *Fatty degeneration.* Fatty degeneration is the commonest form of medial degeneration. The causes resemble those of atheroma. The most obvious proofs of its causation by toxins are afforded by the fatty medial degeneration of arterioles in cases of poisoning by bacterial toxins and endogenous or exogenous non-bacterial toxins. That it is caused by lack of nourishment is shown by its occurrence in the arterioles in cases of severe anaemia. It is the most frequent form of medial degeneration which occurs in old age, or complicates cardiovascular hypertrophy. In focal atheroma fatty degeneration is frequently found in the zone of media immediately external to the affected intima. The fat in fatty degeneration of the media is usually found in the form of small granules; in very exceptional cases a true atheromatous mass involves the media.

Fatty medial degeneration is frequently followed by calcareous impregnation, and this is especially liable to occur in particular arteries. This combination of fatty degeneration and calcification is discussed in the next section.

2. *Calcification associated with fatty degeneration.* This condition is most easily recognized in the muscular arteries. Here it gives rise to hard plaques, which as they increase in size come to have their long axis at right angles to that of the vessel. In advanced stages the plaques make the artery, when viewed either from the outer or inner surface, resemble a 'goose's trachea'. The plaques are concave on the intimal and convex on the outer surface, unless the vessel is distended artificially. Viewed from the intimal surface the plaques are translucent and slaty; if numerous, they are separated by a reticulum of yellow lines of atheroma. On longitudinal section of the artery they are visible as opaque, white dots in the glistening muscle of the media. The femoral, tibial, and radial arteries are most commonly affected. The condition may affect the smallest muscular arteries; thus I have found it in the interlobular arteries of the kidneys.

Microscopically, the calcification is seen to originate, as a rule, in the centre of the media. In addition to calcification, finely granular, fatty degeneration is visible in sections stained by sudan, especially in longitudinal sections. In the advanced condition the affected area becomes occupied by a large mass of calcium. The calcification in many cases has a special affinity for the elastic fibres. Early plaques, in the femoral artery for instance, may consist almost entirely of a network of calcified elastic fibres. Calcified elastic fibres may ramify from the margins of areas of advanced calcification. Portions of the internal elastic lamella are frequently calcified, and calcification in places may be confined to small masses lying on each side of a calcified portion of the lamella.

This form of medial degeneration was first described in detail in the peripheral arteries by Mönckeberg in 1903 (8). It is, in consequence, frequently called '*Mönckeberg's degeneration*'. The formation of calcareous plaques such as were described by Mönckeberg is rare in the aorta. An essentially similar, but more diffuse and less intense calcification is, however, exceedingly common. It is found, in greater or less degree, almost constantly in subjects over forty years of age. In microscopic sections, in the centre of the media, there is an infiltration by granules of calcium associated with a finely granular, fatty degeneration. The infiltration is patchy in intensity, being greatest in lozenge-shaped areas between the elastic lamellae. Its distribution throughout the centre of the media is, however, very diffuse. The areas are very easily decalcified. Thus if haematoxylin preparations are differentiated with 1 per cent. acid alcohol, very few calcium granules remain. The picric acid in van Gieson's stain quickly removes the granules. In the absence of calcium granules the degeneration may be suspected on observing an absence of muscle fibres and an increase of interstitial tissue in the more central portions of the media. Kossa's silver nitrate method demonstrates the calcification well. In an aorta affected by the above diffuse, slight calcification, there may be areas occupied by calcareous plaques similar to those which are characteristic of Mönckeberg's degeneration in the peripheral arteries.

The causes of medial calcification appear to be very similar to those of pure fatty degeneration. The condition is certainly associated with senility. It has been caused experimentally in animals, especially rabbits, by various toxins (Klotz, 1906 (9)). There is evidence in human pathology that certain toxins induce it. Thus, I have found Mönckeberg's degeneration very frequently in diabetes; it is a very important factor in the causation of gangrene of the extremities in chronic diabetes. It is commoner in males than females, and is more liable to occur when the blood-pressure is abnormally high. It is, therefore, a frequent complication of cardiovascular hypertrophy after the third decennium. I have found no evidence that syphilis is a cause.

3. *Mucous degeneration.* The media may be the seat of a mucous degeneration, with which a slight calcareous impregnation is usually associated. In the aorta elastic lamellae become separated by haematoxophil, lozenge-shaped areas, which are deeply stained by muci-carmin. Swollen muscle cells lie in the mucous matrix in some of the areas; in others they are absent. This form of degeneration is rarer than the two described above. I have found it most frequently as a complication of cardiovascular hypertrophy. In such cases it is likely to be associated with the other medial degenerations described above. I have also found it in cases in which there was no evidence of an excessive blood-pressure, and in which there was no other degeneration except a few minute 'flecks' of fatty atheroma. I have obtained no evidence that syphilis causes this form of degeneration.

4. *Medial fibrosis.* Medial fibrosis, when it is an expression of degeneration, is merely an end result or accompaniment of the degenerations described above.

If special stains are employed granules of fat or calcium are usually found in areas which in sections stained by haematoxylin-eosin or van Gieson's method appear to be merely fibrotic. It has been pointed out above that areas of diffuse calcification are quickly decalcified if even dilute acids are employed. The fibrosis usually appears to be relative and not actual. When the muscle fibres degenerate, the interstitial tissue becomes conspicuous. If the degenerate artery suffers aneurysmal dilatation the interstitial tissue is compressed and appears abnormally dense. Further, the collagen fibres may become stouter through hyaline degeneration. In very severe degeneration, however, a proliferation of fibroblasts gives evidence of an actual increase in interstitial tissue. Such fibrosis is easily differentiated from inflammatory fibrosis; in degeneration the fibres retain their normal arrangement, in inflammation the newly-formed fibres course in various directions.

In severe degenerations of the intima or media of large vessels an ingrowth of capillaries, surrounded by infiltration, may take place. This is especially noticeable where there is much debris, or permeation of blood into the media; in the latter case cells containing granules of iron pigment are found. The infiltration is usually very slight, plasma cells are rare, and the elastic lamellae do not show erosion on either side of the perivascular infiltration. This secondary inflammation can, therefore, be differentiated from a chronic syphilitic inflammation. Calcareous atheroma, or calcareous deposits in the media, may excite a metaplastic formation of bone and marrow. Such changes are preceded by an ingrowth of vessels.

Relation of Medial Degeneration to Heightening of the Blood-pressure.

The arguments which have been given above (pp. 208-9) to show that atheroma is not the cause, but is liable to be a secondary complication, of high blood-pressure, apply with equal force to medial degenerations.

The Correlation between Atheroma and Medial Degeneration.

As a general rule, the severer the medial degeneration the greater the atheroma. To this rule, however, there are many exceptions. Intimal and medial degeneration may occur independently. Atheroma frequently occurs when there is no microscopic evidence of medial degeneration. When there is medial degeneration there is almost invariably intimal hypertrophy, but this hypertrophy may show little microscopic and no macroscopic degeneration. Severe medial degeneration may be associated with a greatly hypertrophied intima, in which true atheroma is absent but 'intimal fibrosis' is extensive. In Mönckeberg's degeneration of the peripheral arteries intimal hypertrophy and degeneration are not confined to areas in which there are calcareous plaques; they occur as frequently, often more frequently, over areas of intervening media.

The probable explanation of this is that the artery in an area of extensive calcification is immobile. In the intervening areas the artery is physiologically active, and hypertrophy of the intima is induced. Inasmuch, therefore, as hypertrophied areas of intima are most liable to degeneration, the atheroma is found chiefly in intervals between rigid areas. Finally, the relation between medial degeneration and atheroma varies in different arteries.

It is clear, therefore, that estimations of the amount of medial degeneration based upon the extent of atheroma can only be made with reserve.

PART III.

AMYLOID INFILTRATION.

The media of the arteries within organs is especially liable to affection in cases of lardaceous disease. The amyloid deposit is extra-cellular, and the process is an infiltration rather than a degeneration. Lardaceous disease is not confined to inflammations caused by any special organisms. The incidence of amyloid disease depends, however, upon the nature of the infecting organism in so far as the duration of the inflammatory process is a most important factor. Consequently the disease is most liable to occur in infections by organisms which cause chronic inflammation. It is, therefore, most frequently associated with the specific granulomata: actinomycosis, tuberculosis, syphilis, and Hodgkin's lympho-granuloma. The inflammations caused by pyogenic organisms alone are seldom of prolonged duration; under certain circumstances and in particular situations they are, and then lardaceous disease is very likely to occur. Instances of positions which render pyogenic inflammation liable to be prolonged are dilated bronchi, and bones. Further, loss of albumen from the body, and particularly the formation of pus, appear to be most important factors in determining the incidence of the disease. Lardaceous disease has been caused experimentally by prolonged aseptic suppuration. Lardaceous disease is, therefore, most common in granulomata when there is much inflammatory exudation and suppuration; for instance, in actinomycotic infection, which causes more suppuration than the other specific granulomata, and in tuberculosis of the spine accompanied by psoas abscess. Prolonged suppuration is particularly liable to occur when a pyogenic infection is added to a specific granulomatous inflammation. Thus, in tuberculosis of the lungs lardaceous disease is most liable to occur when there is cavitation, in tuberculosis of joints and bones when sinuses have been formed, and in syphilis when there is gummatous ulceration on the surface of the body. The rarity of the disease in one specific granuloma, rheumatism, is explained by the relatively small distribution of the lesions and the complete absence of suppuration. The following analysis of the cases of lardaceous disease in the years 1907 to 1913 illustrates these points.

The observation that lardaceous disease has become relatively infrequent in recent years is doubtless explained by the great improvements in the arrest of chronic inflammations and ulcerations.

In 7,924 examinations of the body in the years 1907 to 1913 general lardaceous disease was found in 44, i.e. 0.55 per cent.

The lardaceous disease was caused apparently by the following conditions :

1. *Tuberculosis*. 18 cases.

a. Active, chronic, pulmonary phthisis with cavities bounded by fibrous tissue, and, except in one case, with intestinal ulceration : 8 cases.

b. Tuberculosis of the spine ; in one case complicated by psoas abscess, in another by tuberculous ankylosis of the hip : 5 cases.

c. Tuberculosis of the hip ; in one case complicated by chronic pulmonary phthisis with cavitation : 3 cases.

d. Tuberculous pyonephrosis : 1 case.

e. Tuberculous peritonitis : 1 case.

Incidence per cent. in tuberculous affections. Pressure of work has prevented me from estimating the total number of tuberculous cases between 1907 and 1913, but in the years 1908 to 1910 there were tuberculous lesions in 1,199 cases.

Eight of the above cases of lardaceous disease fell within these years ; the incidence was, therefore, 0.66 per cent.

In the years 1907 to 1913 there were 129 cases of *chronic pulmonary phthisis* in which there were cavities bounded by fibrous tissue, and evidence of active tuberculosis in the lungs. Tuberculous ulceration of the intestine was present in 51. The incidence of lardaceous disease in chronic pulmonary phthisis, thus defined, was therefore 6.2 per cent.

In these years there were 17 cases of *tuberculosis of the spine*, 3 being complicated by psoas abscess, 1 by tuberculosis of the knee, 1 by tuberculosis of the thumb, and 1 by ankylosis of the hip. The incidence of lardaceous disease in these 17 cases was 29.4 per cent.

There were 18 cases of *tuberculosis of bones and joints*, in which the spine was not involved. One case was complicated by chronic pulmonary phthisis with cavitation. Lardaceous disease occurred in 16.6 per cent.

2. *Hodgkin's disease*. 3 cases.

In 1 of these cases there was uncomplicated Hodgkin's granuloma ; in 2, tuberculosis was a complication.

Incidence per cent. Lardaceous disease was present in 3 out of 25 cases of Hodgkin's disease, i.e. 12 per cent.

It was present in 1 out of 22 cases of pure Hodgkin's granuloma, i.e. 4.5 per cent.

It was present in 2 out of 3 cases complicated by tuberculosis, i.e. 66.6 per cent.

3. *Actinomycosis*. 3 cases.

Incidence per cent. Lardaceous disease was present in 3 out of 9 cases, i.e. 33 per cent.

4. *Chronic purulent bronchiectasis*. 3 cases.

In one of these cases a calcareous nodule was present in the right apex.

Incidence per cent. In 1907 to 1913 there were 62 cases of chronic bronchiectasis which resembled the above, in that collapse and fibrosis of the intervening tissue were present. In 14 there was evidence of obsolete phthisis. In making this selection, cases of active phthisis, of acute bronchiectasis, and slight

bronchiectasis in chronic bronchitis, and cases in which bronchiectasis was confined to a small portion of a fringe of one lung were excluded. In chronic bronchiectasis, thus defined, lardaceous disease was present in 4·8 per cent.

5. *Syphilis*. 6 undoubted and 1 doubtful case.

Case I. F., 22. Two subperiosteal gummata on calvaria. Scar of old gumma on leg.

Case II. F., 50. Scars of old gummata on leg.

Case III. F., 36. Gummata in liver. Scarred nostrils. Perforation of nasal septum.

Case IV. M., 38. Large scar with pulmonary arteritis in lung. Fibrosis of both testicles. Small scar on penis.

Case V. F., 44. Chronic septic syphilitic ulcer of leg, with thickening of subjacent fibula.

Case VI. F., 32. Large 'paper' scars on legs and thighs.

(Case VII. M., 35. Gummata in liver, an old arthrectomy of right shoulder, and calcareous nodules in the bronchial glands. The arthrectomy may have been performed for tuberculosis; it is, therefore, not admissible to include this case in estimating the incidence per cent. of lardaceous disease in syphilis.)

Incidence per cent. in syphilis; 1908 to 1913. The first of the above six cases occurred in 1907; in the years 1908 to 1913, therefore, lardaceous disease was caused by syphilis in 5 out of 288 necropsies in which 'acquired' syphilitic lesions were present, i. e. 1·73 per cent.

If the cases of so-called congenital syphilis are added, i. e. 10 cases in infants who died under nine months and 4 cases in children and young adults, the incidence is reduced to 1·65 per cent.

If 41 additional cases are included, in which there were skin scars of possible syphilitic origin, the percentage is reduced to 1·45 per cent.

6. *Chronic periproctitis*. 2 cases.

In one case there was also chronic pericolicitis of the descending colon. In the case of pure periproctitis syphilitic infection was denied, and the Wassermann reaction, tested during life, proved negative. In the case with chronic pericolicitis the trouble commenced with a fistula which was operated on twice, i. e. twenty-seven and twenty-four years before death. The only evidence of syphilis was a statement by the patient that he had had gonorrhoea and a 'chancre'; the date given in this history was thirty-nine years before death.

7. *Anal fistula and rectal abscess*, 1 case. The fistula was first observed thirty-three years before death. 8. *Pyonephrosis*, 1 case. 9. *Chronic sinus and hepatic abscess following appendicectomy*, 1 case. 10. *Chronic parametric abscess*, 1 case. 11. *Rheumatoid arthritis and exfoliative dermatitis*, 1 case. 12. *Chronic rheumatic endocarditis; progressive endocarditis, with streptococcal bacteraemia*, for over four months, 1 case. 13. *Acute and chronic rheumatic endocarditis*, 1 case. 14. *No cause ascertainable*, 1 case.

PART IV.

INFLAMMATIONS.

The arteries may be infected from their intima, either by micro-organisms settling upon the surface or by the arrest of infective emboli within their lumen. They may also be infected by micro-organisms reaching the media or adventitia by the vasa vasorum, or by direct inward spread of inflammation from the surrounding tissues.

Inflammation of the arteries, 'arteritis', may be differentiated into 'endarteritis', 'mesarteritis', and 'periarteritis' according to whether the intima, media, or adventitia is affected.

Inflammation of the arteries may be caused by probably all the micro-organisms which excite inflammation in other tissues. Certain micro-organisms excite in the tissues reactions which usually have outstanding histological peculiarities: such reactions occur in syphilis, tuberculosis, leprosy, rheumatism, and Hodgkin's disease. In the reactions excited by a second group of micro-organisms distinctive characters in the histological pictures are less precise. It is convenient in the case of the arteries to adhere to the custom of describing separately the reaction to each micro-organism of the former group, whilst a single, general description is given of the reactions to those of the latter group. Unfortunately, this distinction, between reactions which are peculiar to the infecting micro-organism and those which are not, is relative and not absolute; consequently there are no unequivocal terms by which the distinction can be denoted. The inflammations caused by the first group of micro-organisms are generally designated '*specific granulomatous inflammations*'; I shall, therefore, call those of the second group '*non-granulomatous*', in the absence of any less objectionable term.

The appearances caused by inflammation differ in arteries of different size. It is, therefore, convenient to treat separately (A) the large elastic arteries, and (B) the muscular and small elastic arteries. The small elastic arteries are represented by the branches of the pulmonary arteries.

A. *Inflammation of the large Elastic Arteries.*

1. *Endarteritis.* Inflammation confined to the intima of the large elastic arteries is very rare. The intima of the aorta may be infected in cases of septicaemia and pyaemia: this occurs most commonly in cases of malignant endocarditis, and the ascending aorta is usually affected. The endoaortitis is indicated by the presence of vegetations upon the intima. In such infections, however, the inflammation rapidly involves the subjacent coats. Tuberculous endarteritis, intimal tuberculosis, of the large elastic arteries is very rare. An example occurred in the abdominal aorta close to the coeliac axis, in a child

of thirteen, in a necropsy in 1910. There is evidence that spirochaetes may invade the aorta from the intimal surface, but I have not seen a syphilitic inflammation which was confined to the intima of a large elastic artery.

In inflammations of the large elastic arteries usually two or more coats are involved. For convenience the single term *arteritis* may be employed to denote these combinations of mesarteritis with endarteritis and periarteritis.

2. *Arteritis. Non-granulomatous arteritis* of large elastic arteries, other than the aorta, is usually caused by infective embolism or by spread of purulent inflammation from the surrounding tissues. The carotids are especially exposed to the latter mode of infection. In the aorta the infection usually originates in an endoarteritis, or in embolism of the vasa vasorum; the root of the aorta may also be infected by spread from a pericarditis. Infection of the aorta may occur in any septicaemia or pyaemia, but is most frequently a complication of malignant endocarditis. The commonest infecting organisms are streptococci and staphylococci. The characteristic feature of the inflammatory reaction is an infiltration with neutrophil leucocytes. In the severer infections areas of the aortic wall are completely replaced by masses of neutrophil leucocytes; in the less severe infections fibroblastic proliferation is conspicuous and the neutrophil leucocytes are associated with eosinophil leucocytes, plasma cells, and lymphocytes. The arterial wall may rupture or an aneurysm may be formed.

The following examples of non-granulomatous arteritis of large elastic arteries occurred at necropsies during the years 1908 to 1913 inclusive:

Non-granulomatous aortitis. 5 cases.

1. Male, 25. Aortitis with formation of small saccular aneurysm, covered by vegetations, involving the aortic commissure and sinus of Valsalva of the anterior aortic cusp. Ulcerative endocarditis of the cusps of the aortic valve, the pars membranacea septi, and the contact margin, chordae tendineae, and aortic surface of the mitral valve. History of nine weeks' illness.

2. Male, 66. Aortitis with formation of saccular aneurysm, one inch in diameter, in the ascending aorta, three inches above the commissure. Ulcerative endocarditis of mitral valve. History of thirteen weeks' illness.

3. Male, 24. Aortitis with formation of small saccular aneurysm in the commissure immediately above the orifice of the right coronary artery. Small fibrinous vegetation on edge of aneurysm. Ulcerative endocarditis of cusps of aortic valve and ventricular surface of aortic cusp of mitral valve. History of eighteen weeks' illness.

4. Male, 35. Aortitis with formation of small saccular aneurysm immediately above the commissure. Vegetations and a perforation into the pericardial sac at the distal extremity of aneurysm. Healed endocarditis of aortic valves. Congenital stenosis of aorta, admitting only a fine probe, at site of closed ductus arteriosus. Illness commenced with sweating and fever seventeen weeks before death.

5. Female, 18. Aortitis beneath organizing thrombus at site of closed ductus arteriosus. Multiple organized, organizing, and recent thrombi in veins and arteries. Chronic septic spleen. Chronic otitis media. Signs of sinus thrombosis two years before death.

Non-granulomatous arteritis of other large elastic arteries. 4 cases.

In all cases the inflammation spread from surrounding abscess or cellulitis. The right internal carotid was involved, near its origin, in 2 cases; the left internal carotid, near its origin, in 1 case; the right external carotid, near its origin, in 1 case.

Rheumatic arteritis. In cases of rheumatic endocarditis microscopic granulomatous foci may be present in the adventitia and media of the origin of the aorta. I have not, however, seen a case in which the lesions have led to macroscopic changes in the artery.

Tuberculous arteritis of the large elastic arteries is very rare. It is commonest in the aorta, and may give rise to macroscopic appearances which are identical with those caused by syphilitic infection. In places the microscopic picture may also resemble syphilitic arteritis closely. The differential diagnosis depends upon the discovery of areas of typical tuberculous granulation tissue, and upon the identification of tubercle bacilli.

During the period 1908 to 1913 there was only one example of tuberculous arteritis of a large elastic artery.

Tuberculous aortitis. 1 case.³

Male, aged 32. Tuberculous inflammation of the abdominal aorta; scarring of the aorta in the neighbourhood of the coeliac axis; large sacular aneurysm extending from two centimetres below the coeliac axis to two centimetres above the aortic bifurcation. Rupture of the aneurysm into the duodenum. Caseous and granulomatous tuberculosis of the lumbar, coeliac, pancreatic, iliac, inguinal, superior and posterior mediastinal, left axillary, left supraclavicular, and left cervical lymphatic glands. A few calcareous nodules in coeliac, pancreatic, and iliac lymphatic glands. Calcareous nodules in glands of right bronchus and a gland of tracheal bifurcation. Caseo-calcareous nodule in the apex, and subpleural calcareous nodule in the hilum, of the upper lobe of the right lung. Focal areas of tuberculous arteritis and periarteritis in kidneys.

The changes in the aorta could only be differentiated by microscopic investigation from those caused by syphilis. The Wassermann test was applied to the serum twice during life, and proved negative on both occasions.

Syphilitic arteritis. Acquired syphilis is far the commonest cause of aortitis, and is the commonest cause of inflammation of the other large elastic arteries near the aorta. Syphilitic aortitis is not only the commonest inflammation of the aorta, but it is the lesion of acquired syphilis which is found most frequently in the post-mortem room of a general hospital. Syphilitic inflammation of the other large elastic arteries is a relatively frequent lesion. These points are illustrated by the analysis of our necropsies for the years 1908 to 1913 inclusive.

In these years there were 288 necropsies in which lesions of 'acquired' syphilis were present, if 53 cases of fibrosis of the testicles alone are admitted as syphilitic. In these 53 cases there was no other explanation of the fibrosis; 4 were accompanied by alopecia.

³ A report of this case has been published by Dr. E. A. Tozer, in the *British Medical Journal*, Dec. 12, 1914, p. 1022.

The lesions in these 288 necropsies were as follows:

Syphilitic aortitis	175, i. e.	60.76 %
Fibrosis or gummata of testicles	117, "	40.62 %
Scars on penis, ⁴ associated with syphilitic lesions in other organs, and one gumma on penis	61, "	28.12 %
Syphilitic endocarditis of aortic valves	45, "	15.62 %
Gummata or undoubted syphilitic scars of skin	44, "	15.27 %
Arteritis of large elastic arteries, other than aorta	43, "	14.93 %
Gummata or syphilitic fibrosis of liver	23, "	7.98 %
Meningitis	9, "	3.12 %
Other syphilitic lesions of brain and cord	7, "	2.43 %
Arteritis of large muscular arteries	6, "	2.08 %
Gummata or scars of epiglottis	6, "	2.08 %
Arteritis of large cerebral arteries	4, "	1.38 %
Scars of nose or perforation of septum	4, "	1.38 %
Scars or broncho-pneumonia of lungs	3, "	1.04 %
Myocarditis	3, "	1.04 %
Scars or perforation of palate	3, "	1.04 %
Scars of pharynx	3, "	1.04 %
Gummata of larynx	2, "	0.69 %
Gummata or chronic hypertrophic inflammation of bone	2, "	0.69 %
Gummata of pancreas	1, "	0.34 %
Gummata of lymphatic glands	1, "	0.34 %
Gummata of retroperitoneal tissues	1, "	0.34 %

In Table I are enumerated the syphilitic lesions, in other organs and tissues, which were associated with the aortitis; scars on the penis and alopecia are added to the specific lesions.

The vertical columns indicate the nature and the site of the lesions. The cases are set out in horizontal columns. Identical cases are grouped and set out in a single horizontal column, a numeral indicating their number. Addition of the numbers in the vertical columns gives the frequency with which the respective lesions were associated with the aortitis.

The sites in the aorta which were affected by syphilitic inflammation are given in Table II. The large elastic arteries, other than the aorta, which were the seat of syphilitic inflammation are enumerated in Table III.

Tables II and III are arranged in the same manner as Table I. Addition of the numbers in the vertical columns gives the number of times in which each particular site was affected.

⁴ Scars on the penis cannot be regarded as specific syphilitic lesions. It is, however, of value to the clinician to recognize the frequency with which such scars are associated with syphilitic infection. In the years 1908 to 1913 scars were present on the penis in 75 cases. The number of cases which were associated with syphilitic lesions is given above; there were, therefore, 15 cases in which the scars were not accompanied by specific syphilitic lesions. In 1 of these 15 cases the patient had given a history of having contracted syphilis forty-eight years before death; in 1 the Wassermann test, applied after death, reacted positively; in 1 the test, applied both before and after death, reacted negatively; in 1 the test, applied after death, reacted negatively. In the remaining 11 cases inquiry regarding syphilitic infection is not mentioned in the clinical notes, and no Wassermann test had been applied.

TABLE I. *Syphilitic Lesions, Scars on the Penis, and*

Number of cases.	Aortitis.	Arteritis of branches of aorta.	Aortic endocarditis.	Testicle, fibrosis.	Testicle, gumma.	Testicle, previous excision.	Penis, scars.	Skin, scars.	Liver, syphilitic fibrosis.	Liver, gumma.	Myocarditis.	Pulmonary artery, arteritis.
47	47	—	—	—	—	—	—	—	—	—	—	—
2	2	—	—	—	—	—	—	—	—	—	—	—
11	11	11	—	—	—	—	—	—	—	—	—	—
1	1	1	—	—	—	—	—	1	—	—	—	—
3	3	3	—	3	—	—	—	—	—	—	—	—
2	2	2	—	—	—	—	2	—	—	—	—	—
1	1	1	—	—	—	—	1	—	—	—	—	—
1	1	1	—	1	—	—	1	—	—	1	—	—
1	1	1	—	1	—	—	—	—	—	—	—	—
1	1	1	—	1	—	—	1	—	1	1	—	—
1	1	1	—	—	—	—	1	1	—	—	—	—
1	1	1	—	—	—	—	—	1	—	—	—	—
1	1	1	—	—	—	—	—	—	—	—	—	—
3	3	3	3	—	—	—	—	—	—	—	—	—
1	1	1	1	1	—	—	—	—	—	—	—	—
2	2	2	2	—	—	—	—	2	—	—	—	—
1	1	1	1	—	—	—	—	—	—	—	—	—
1	1	—	—	—	—	—	—	—	—	—	—	1
23	23	—	23	—	—	—	—	—	—	—	—	—
1	1	—	1	1	—	—	1	—	—	—	—	—
1	1	—	1	1	—	—	—	—	—	—	—	—
5	5	—	5	—	—	—	5	—	—	—	—	—
2	2	—	2	—	—	—	—	2	—	—	—	—
1	1	—	1	—	—	—	1	1	—	—	—	—
1	1	—	1	—	—	—	—	—	1	—	—	—
1	1	—	1	1	—	—	1	—	1	—	—	—
2	2	—	—	—	—	—	—	—	—	—	2	—
1	1	—	—	1	—	—	—	—	—	—	1	—
13	13	—	—	13	—	—	—	—	—	—	—	—
1	1	—	—	1	—	—	—	—	—	—	—	—
2	2	—	—	2	—	—	2	—	—	—	—	—
1	1	—	—	1	—	—	1	1	—	—	—	—
1	1	—	—	1	—	—	1	1	1	—	—	—
3	3	—	—	3	—	—	—	3	—	—	—	—
1	1	—	—	1	—	—	—	1	—	—	—	—
1	1	—	—	1	—	—	—	—	—	—	—	—
2	2	—	—	—	2	—	2	—	—	—	—	—
1	1	—	—	—	—	1	—	—	—	—	—	—
15	15	—	—	—	—	—	15	—	—	—	—	—
2	2	—	—	—	—	—	2	2	—	—	—	—
1	1	—	—	—	—	—	1	—	—	—	—	—
1	1	—	—	—	—	—	—	—	—	—	—	—
8	8	—	—	—	—	—	—	8	—	—	—	—
1	1	—	—	—	—	—	—	1	—	—	—	—
175	175	92	42	34	2	1	39	24	4	2	3	1
%	100	18.3	24.0	19.4	1.14	0.57	22.3	13.7	2.28	1.14	1.71	0.57

Alopecia, associated with Syphilitic Aortitis, 1908 to 1913.

Broncho-pneumonia.	Epiglottitis, scars.	Larynx, gumma.	Lymphatic glands, gumma.	Pancreas, gumma.	Retroperitoneal tissue, gumma.	Leptomeningitis.	Cerebral arteries, arteritis.	Pachymeningitis interna haemorrhagica.	Tabes dorsalis.	Cranial nerves, atrophy.	Alopecia.
1	4	1	1	1	1	3	2	1	1	1	8
0.57	2.28	0.57	0.57	0.57	0.57	1.71	1.14	0.57	0.57	0.57	4.57

TABLE II.

Sites of Syphilitic Aortitis, 1908 to 1913.

Number of Cases.	Commissure.	Ascending thoracic.	Arch.	Descending thoracic.	Abdominal.
34	34	34	34	34	—
23	—	23	23	23	—
17	17	17	—	—	—
15	15	15	15	—	—
14	14	14	—	14	—
13	13	13	13	13	13
12	—	12	12	—	—
9	—	9	—	9	—
8	—	8	8	8	8
6	—	—	6	6	—
6	—	6	—	—	—
4	—	—	—	4	4
3	—	—	—	3	—
2	2	2	—	2	2
2	2	2	2	—	2
2	2	2	—	—	2
2	—	—	2	—	—
1	—	1	1	—	1
1	—	1	—	1	—
1	—	1	—	1	1
175	99	160	116	118	33

TABLE III

Large Elastic Arteries, other than Aorta, affected by Syphilitic Arteritis, 1908 to 1913.

Number of Cases.	Innominate.	Subclavian.		Common carotid.		Pulmonary stem.	Pulmonary branch to right lower lobe.
		Right.	Left.	Right.	Left.		
16	16	—	—	—	—	—	—
3	3	—	3	—	—	—	—
3	—	—	3	—	—	—	—
2	2	2	2	—	—	—	—
1	1	—	1	1	1	—	—
1	1	—	1	—	1	—	—
1	—	—	—	1	1	—	—
1	—	—	—	1	—	—	—
1	—	—	—	—	—	1	—
1	—	—	—	—	—	—	1
30	23	2	10	3	3	1	1

Table II shows that syphilitic inflammation attacked the ascending thoracic aorta more frequently than any of the other segments of the aorta.

In the cases enumerated in Table III syphilitic aortitis was also present, except in the case of arteritis of the pulmonary branch to the right lower lobe.

Histology of Syphilitic Inflammation of the Large Elastic Arteries.

The histological changes seen in the aorta may be taken to illustrate syphilitic arteritis of the large elastic arteries. The histological picture varies according to the stage of the inflammatory process.

1. In the *early stages* the reaction shows in amount and character variations which are similar to those found in other organs. Most commonly there is a moderate perivascular infiltration of the adventitia, which extends along capillaries into the media. There is not only an increase in the number of capillaries in the affected portion of the media, but the capillaries pass abnormally far towards the intima. In the majority of cases their branches are especially numerous at the junction of the media with the intima; usually some branches penetrate the intima. In the zone of infiltration round the capillaries the muscle fibres and elastic lamellae of the media are replaced by spindle fibroblasts; the elastic lamellae end abruptly at the outer edge of the infiltration, their ends being swollen and stained abnormally dark by Weigert's elastin. Rarely, the infiltration replaces large patches of the media. The majority of the cells of the infiltration are plasma cells; lymphocytes, a few eosinophil leucocytes and, occasionally, neutrophil leucocytes are also found; giant cells are relatively rare. Areas of necrosis in the neighbourhood of the infiltration are not uncommon. True gummata, that is to say focal areas of caseation surrounded by a zone of infiltrated granulation tissue, are very rare; we have not obtained a single example in over seven years.

In the more acute and intense reactions a typical arteritis, with endarteritis, of the vasa vasorum (*vide* p. 230) may be present. In the commoner, more chronic reactions it is very unusual to find an arteritis of the vasa vasorum. The arteries are frequently narrowed by intimal thickening, but the intimal thickening has the structure of a hypertrophy. Within the internal limiting elastic lamella are three or four zones of muscle fibres, which are chiefly longitudinal in direction; the zones are separated by layers of elastic.

The intima of the aorta is usually thickened over the areas of inflammation. Rarely, this thickening is a pure hypertrophy of the musculo-elastic and hyperplastic layers. Such pure hypertrophy is found in cases in which the inflammation of the media is slight and does not extend into the intima. Usually, the thickening is, in its central part or in its full extent, inflammatory. That is to say it is an endarteritis. It then consists of a vascularized granulation tissue in which the cells are arranged irregularly, and musculo-elastic and hyperplastic layers cannot be recognized. In some of the most intense reactions the intima is greatly infiltrated and is covered by a deposit of fibrin.

The inflammatory thickening of the intima in the early stages can usually be distinguished with the naked eye from atheromatous thickenings by (1) its greater latitude and prominence, (2) pearly colour, (3) rubbery consistence, (4) crenated outline, (5) pitted surface, and (6) almost complete freedom from fatty or calcareous degeneration.

2. *Late stages.* The cellular granulation tissue develops into dense, fibrous, scar tissue in which only delicate elastic fibrils are present. Fortunately for histological diagnosis, the progressive nature of the inflammation ensures that infiltrated areas are almost invariably present, even when scar tissue has been formed.

Degeneration of the intima is, as has been said above, usually though not invariably, insignificant in the early stages of the inflammation. In the late stages, fatty degeneration and calcification occur almost invariably. The changes are most conspicuous in areas of thickened intima which have not become thinned by aneurysmal dilatation. The degeneration and calcification in such areas are usually very severe. The calcification tends to appear first in the inner layers of the intimal thickening. Fatty, atheromatous degeneration usually appears in the external part of the intima. Atheroma, as defined in this paper, is, therefore, a complication of the syphilitic inflammatory process. If the term 'syphilitic atheroma' is employed at all, it must be confined to an atheroma which covers areas of syphilitic arteritis.

Replacement of the elastic and muscle of the media by granulation or scar tissue weakens the wall so that dilatations, varying from minute linear, often stellate, sulci to large aneurysms, are very frequently produced. The presence of stellate or longitudinal sulci, or definite saccular aneurysms, affords the most valuable clue towards the recognition of the condition macroscopically. The slight wrinkling of the intima which is seen sometimes between adjacent atheromatous buttons must not be confused with such sulci. Further, it must be remembered that, as is shown in Part VI, pp. 236-8, non-syphilitic inflammations and severe medial degenerations give rise occasionally to similar appearances.

An arteritis similar to that described above may occur as a late manifestation of 'congenital syphilis'. This was the case in a girl aged 7 and a girl aged 17 (Turnbull, 1911 (10)). Wiesner, 1910 (11), considers that infiltration of the outer layers of the media, and to a less extent of the adventitia, is commonly present in the aorta and the other large elastic arteries of syphilitic children who have died soon after birth. In the few cases examined in this Institute such infiltration has not been found.

The Dangers to Life of Syphilitic Arteritis of the Large Elastic Arteries.

These are illustrated by the following statistics for the years 1908-13.

Death was caused by *syphilitic aortitis* in the following ways :

(1) Implication of the aortic valves in the inflammation	27 cases.
(2) Stretching of the affected commissure	8 "
(3) Rupture of aneurysms	25 "
(4) Pressure of aneurysms on trachea or bronchi leading to collapse of lung and broncho-pneumonia	9 "
(5) Pressure of aneurysms on pulmonary artery	2 "
(6) Infarction of heart following involvement of orifices of coronaries by aortitis	8 "
(7) Embolism into coronary artery	2 "
(8) Embolism into cerebral arteries	2 "
(9) Embolism into superior mesenteric artery	1 "

The emboli in the above cases arose from fibrin upon the surface of intensely inflamed intima in 3 cases; from thrombi formed in hearts dilated as the result of stretching of the implicated commissure in 2 cases. Emboli may also arise from fibrin deposited within aneurysmal cavities.

Although constriction of the coronary orifices was the cause of death in only 8 cases, marked narrowing or complete occlusion was present in 27 cases; the right orifice was affected in 11, the left in 3, and both in 13 of these cases.

Death was caused by *syphilitic arteritis of the other large elastic arteries* in the following way:

Rupture of aneurysms of the right common carotid and left subclavian arteries into the cervical tissues and oesophagus respectively: 2 cases.

In this list there is no instance of rupture of the aorta during syphilitic inflammation, before the formation of true aneurysm. I have not yet seen such a case.

Results of Wassermann Tests in Syphilitic Aortitis, 1908 to 1913.

The Wassermann reaction of serum, obtained either before or after death, was tested in forty-two of the cases in which aortitis was diagnosed. It is important in this connexion to remember that the diagnosis depended upon the presence of an active inflammatory reaction. The particulars of the cases and the results of the tests are set out in Table IV.

For tests made during life I am indebted to Dr. Paul Fildes and Dr. P. N. Pantou. Dr. Fildes (12) used Wassermann's original technique with the addition of cholesterin to the alcoholic antigen; Dr. Pantou employed Fleming's modification of the original method. For the Wassermann tests made after death I am indebted to Dr. Fildes. Dr. Fildes in 1911 and 1912 made a valuable research in a series of unselected necropsies to ascertain what modification of the original technique is suitable for post-mortem tests. The majority of the post-mortem tests entered in the table occurred in this series.

In Table IV the methods employed in each case are stated. One asterisk is placed in the post-mortem column for each case in which the test had been applied both before and after death. The cases in the table are divided into two groups. In the first group there are 29 cases in which active inflammatory reaction was confined apparently to the aorta, branches springing from the aorta, the aortic valves, and, in one case, the pulmonary stem where it was in contact with the aorta. In the second group, in which there are 13 cases, active syphilitic inflammation was present in tissues other than the aorta and the large arteries.

The first group gives the truest indication of the influence of syphilitic aortitis upon the Wassermann reaction. In 4 cases the serum was tested before death by Wassermann's method; the reaction was positive. In 8 cases the serum was tested before death by Fleming's modification; the reaction was positive in 7 and negative in 1. The latter case had been tested a week before, and the reaction was then doubtful; the histological picture was very characteristic. One of the cases which gave a positive reaction to Fleming's test before death was tested also after death by Wassermann's method and reacted positively. The serum in 17 cases was tested after death alone; in 14 cases the reaction was positive, in 3 it was negative.

TABLE IV.
Wassermann Reactions of Serum in Syphilitic Aortitis, 1908 to 1913.

Number of Cases.	Lesions.	Ante mortem.				Post mortem.	
		Wassermann.		Fleming.		Wassermann.	
		+	-	+	-	+	-
	Active.		Inactive.				
8	Aortitis alone	-	Scar of skin	1	1	4	2
2	Aortitis	-	Scar on penis	-	-	2	-
3	Aortitis	-	Scar of skin, scar on penis	1	-	2	-
5	Aortitis, arteritis of branch	2	Scar of skin, scar of epiglottis	1	-	2	-
1	Aortitis, arteritis of branch	-	Scar of skin	-	-	1	-
1	Aortitis, arteritis of branch, aortic endocarditis	1	Scar of skin	1	-	1	-
2	Aortitis, arteritis of branch, aortic endocarditis	-	Scar of skin	-	-	-	-
1	Aortitis, arteritis of pulmonary artery	1	Scar on penis	1	-	2*	1
3	Aortitis, aortic endocarditis	-	Scar of skin	-	-	1	-
1	Aortitis, aortic endocarditis	-		1	-	-	-
1	Aortitis, aortic endocarditis	-		-	-	-	-
29		4		7	1	15*	3
2	Aortitis, arteritis of branch, fibrosis of testicles	1	Scar of skin	1	-	1	-
3	Aortitis, fibrosis of testicles	1		-	-	1	-
2	Aortitis, fibrosis of testicles	-		1	-	2	-
2	Aortitis, fibrosis of testicles	-		-	-	1	-
1	Aortitis, aortic endocarditis, focal fibrosis of liver	-		-	-	1	-
1	Aortitis, myocarditis	-		1	-	1*	-
1	Aortitis, arteritis of branch, gummata in liver	1	Scar on penis	-	-	1*	-
1	Aortitis, gumma of testicle	-	Scar on penis	-	-	1	-
1	Aortitis, subacute leptomeningitis, atrophy of cranial nerves	-	Scar on penis	-	-	-	-
1	Aortitis, arteritis of branch, hepatic lobatum with gummata, gummata of head of pancreas, adjacent glands, and retroperitoneal tissues, fibrosis of testicles	1		1	-	-	-
13		4		3	-	8**	-
42		8		10	1	23***	3

Of the 13 cases in the second group, 7 cases were tested before death, 4 by Wassermann's method and 3 by Fleming's modification; all 7 cases reacted positively. Two cases tested before death, one by Fleming's and one by Wassermann's method, were tested also after death and again reacted positively. The serum in 6 cases was tested after death alone; all 6 cases reacted positively.

The significance of the results of the tests made *post mortem* cannot be estimated exactly until the particulars of Dr. Fildes' research are published. It may, however, be stated here that Dr. Fildes, when modifying his technique so as to obtain the most reliable results, started with methods which would ensure elimination of a positive reaction in non-syphilitic cases, but which were liable to give a negative reaction when the amount of Wassermann substances in the serum was minimal. Towards the end of the series, however, the technique had been so improved that the test was rendered much more delicate, without any liability to positive results in non-syphilitic cases having been introduced. If the results of the *ante-mortem* tests are alone considered, and if scars of the skin of the penis or of the rest of the body and scars of the epiglottis are regarded as inactive lesions, then the results may be summarized as follows. In 7 cases of aortitis associated with syphilitic inflammation of other organs Wassermann's test was applied in 4 and Fleming's in 3; in all 7 cases the serum reacted positively. In 12 cases in which aortitis was present alone or was only associated with syphilitic inflammation of the aortic valves and of arteries in continuity or contact with the aorta, Wassermann's test was applied in 4 and Fleming's in 7; in one case alone was the reaction negative. This case was tested by Fleming's method; the reaction in a test made a week before was doubtful; the histological picture was very characteristic.

Date of Primary Infection in the Cases of Syphilitic Aortitis.

In the analyses given in this paper the diagnosis of syphilitic aortitis has depended upon the histological picture. Some active reaction was present in all cases. The dates of infection which had been recorded in the clinical histories give, therefore, some indication of the periods after primary infection at which active inflammation may be present.

Histories of previous syphilitic manifestations had been recorded in 34 cases.

In the case of a woman, aged 43, who died on September 25, 1913, the only history of a syphilitic lesion was that of a gummatous ulcer of the leg; the ulcer had appeared in 1902, and after treatment in the infirmary healed in 1906. The following history of parturitions was obtained, however, which suggests that infection occurred between twenty and twenty-three years before death: 1890, healthy female child, alive and well in 1913; 1892, male foetus of 8½ months, lived half an hour; 1893, male foetus of 7½ months, still-born; 1894, female foetus of 7 months, still-born; 1895, male foetus of 7 months, still-born; 1896, male, 'eyes began to water' in autumn of 1912, treated in London Hospital for chronic interstitial keratitis in 1913, Wassermann reaction positive February 1913; 1899, female, healthy 1913; 1902, female, healthy 1913; 1904, female, healthy 1913; 1908, male, being treated in Out-patients' for 'chest trouble' 1913.

In the remaining 33 cases, a history of a chancre had been obtained. In one case no date was recorded, in another case infection was said to have occurred 'many years ago'. The number of years which had elapsed between the primary lesion and death in the remaining 31 cases is as follows:

7, 8 (2), 15 (2), 17, 20 (4), 21 (2), 22 (3), 24 (2), 25 (3), 26 (3), 28, 30, 38, 39, 40 (4).

Three of these cases are remarkable for the relative shortness of the period between infection and the presence of aortitis. A tertiary lesion upon the penis may simulate a primary chancre; thus in 1910 a male, aged 48, was found at necropsy to have a small indurated, gummatous ulcer on the under surface of the foreskin, a gumma in the liver, and fibrosis of both testicles. It is advisable therefore, to quote in full the histories in these three cases: (1) Male, aged 40. 'A chancre', seven years before death; 'no secondary manifestations; treated for three months; black wash applied locally and mercury administered by the mouth'. (2) Male, aged 28. 'A chancre', eight years before death; 'treated for one month; never had gonorrhoea'. (3) Male, aged 36. 'Gonorrhoea' seventeen years before death; 'chancre' eight years before death, 'followed by ulcers in the mouth; no treatment for the syphilis'. These histories do not exclude the possibility that the 'chancre' was gummatous.

In fourteen other cases syphilitic infection had been denied, but a history of *gonorrhoea* had been obtained. The number of years which had elapsed between the gonorrhoeal infection and death is as follows:

12, 15, 18 (2), 20 (4), 26, 30, 31, 40 (2), 42.

Presence of Spirochaeta pallida in Syphilitic Aortitis.

The proof that a lesion is syphilitic depends upon the detection of the presence of the *Spirochaeta pallida*. The late Dr. Aitchison, 1908 (13), in his research on 'mesaortitis and aneurysm' in this Institute, searched for spirochaetes by Levaditi's method of staining; since then we have made sporadic attempts, in cases of aortitis, with the methods of Levaditi and Noguchi, using as controls portions of liver in which spirochaetes were known to be present; recently Dr. Donald has started a systematic research, employing dark-ground illumination. All these attempts have been unsuccessful. Spirochaetes have been demonstrated in aortitis, by Levaditi's method of staining, by Reuter, 1906 (14), Schmorl, 1907 (15), and Homer Wright and Richardson, 1909 (16). The last two investigators found the organisms in no less than five cases. In Reuter's case the spirochaetes were found in the thickened intima only, in the cases of Wright and Richardson they were found in both intima and media. Professor Osler kindly gave me, in 1909, one of the sections of Wright and Richardson. In this section very numerous spirochaetes are present; the inflammatory reaction is more active and intense than that in any of the cases in which we have searched for spirochaetes.

B. *Inflammation of the Muscular and Small Elastic Arteries.*

The small elastic arteries are represented by the smaller pulmonary branches.

1. *Endarteritis.* An endarteritis which is unaccompanied by inflammation of the other coats may occur. This is not uncommon in *tuberculosis*, particularly of the small pulmonary arteries, but is rare in *syphilis*. The histology of the endarteritis is similar to that which accompanies arteritis (*vide infra*).

2. *Periarteritis.* Pure periarteritis is often found in the arterioles of the nerve roots, the leptomeninges, and, particularly, the substance of the brain and cord. It is well illustrated in *polio-encephalo-myelitis*, *syphilis*, and *tuberculosis*. In the early stages the lymphatic adventitial sheath of the arterioles is infiltrated with round cells, of which the majority have non-granular basophile protoplasm. The chief varieties of these cells are described in a paper by McIntosh and Turnbull, 1913 (17). A study of cases of *polio-encephalo-myelitis* has convinced me that these cells with basophil protoplasm are formed by proliferation of the endothelial cells which line the lymphatic channels. In *syphilis* many assume the characteristics of plasma cells; in *tuberculosis* plasma cells are rare; in *polio-encephalo-myelitis* they are exceptional. In *polio-encephalo-myelitis* neutrophil, eosinophil, and, rarely, basophil leucocytes are also found; the neutrophil and eosinophil leucocytes emigrate from the blood and pass through the adventitia into the substance of the cord or brain. The adventitial infiltration may lead ultimately to a thickened, hyaline, fibrotic adventitia which is very conspicuous in sections stained by van Gieson's method. This fibrosis of the adventitia is a feature of the histology of the late stages of less intense syphilitic meningo-encephalitic reactions, for instance in so-called 'syphilitic transverse myelitis' and 'chronic hypertrophic syphilitic meningitis'. The confinement of the inflammation to the adventitia depends upon the relatively slight intensity of the reaction. Thus, in the above syphilitic affections, many arterioles show in addition implication of the media, which is also thickened, hyaline, and fibrotic. Further, in some arterioles evidence of involvement of the intima is shown by fibrotic thickening being present within the elastic lamella. Finally, pure periarteritis may be present in areas of the meninges or of the substance of the spinal cord, when a typical arteritis is present in the cerebral arteries.

3. *Arteritis.* In the great majority of the inflammations of the muscular and small elastic arteries all the coats are involved.

The appearances differ according to the size of the arteries.

(i) *Large muscular arteries.* *Non-granulomatous* inflammation of the larger arteries is usually caused by infective embolism or by spread inwards of inflammation from the surrounding tissues. The wall of the artery is infiltrated with neutrophil leucocytes. The inflammation is usually acute and destructive, leading rapidly to aneurysmal dilatation or direct rupture.

Tuberculous arteritis of the large muscular arteries is extremely rare.

The changes caused by *syphilitic* inflammation of the large muscular arteries may be similar to those described in the large elastic arteries. In our records the only large muscular arteries affected by syphilitic inflammation have been branches of the aorta; the alterations in structure resembled those in the large elastic arteries.

In 1908-13 the following large muscular arteries were affected by syphilis:

The coeliac artery in	2 cases.
The superior mesenteric artery	1 case.
The coeliac and superior mesenteric arteries	1 „
The splenic artery	1 „

In all these cases syphilitic aortitis was also present.

(ii) *Small muscular and elastic arteries.* Non-granulomatous inflammation of these arteries is usually acute and destructive. The wall of the artery is infiltrated with neutrophil leucocytes; destruction of the muscular and elastic fibres leads rapidly to aneurysmal dilatation or direct rupture. An acute caseous, tuberculous, or syphilitic inflammation may cause rapid destruction and rupture. Syphilis and tuberculosis, however, usually cause a more chronic arteritis in which changes in the intima are very conspicuous and produce almost complete occlusion of the lumen. The condition is, therefore, frequently referred to as '*endarteritis obliterans*'. An arteritis of this type may also be caused by pyogenic organisms, and the organisms of various acute infections. It occurs when the inflammation caused by these organisms is of a subacute or chronic character. It is met with considerable frequency in chronic pancreatitis. I have seen it in streptococcal meningitis, and Andrewes (18) mentions its occurrence in the meninges in infection by the *Micrococcus intracellularis meningitidis*. It is, however, much more common in the specific granulomata. It is frequently present in tuberculous lesions, particularly those of the meninges and lungs. In syphilis it is very common.

Endarteritis obliterans is characterised by the appearance of an intimal thickening internal to the elastic lamella and stripe. In the earliest stages round cells are seen between the stripe and the endothelium. Spindle fibroblasts are seen later, a definite granulation tissue having been formed. This granulation tissue usually shows the characteristics of the granulation tissue caused in other tissues by the particular infecting organism. Thus in syphilis plasma cells are usually present and eosinophil leucocytes are common. Giant cells may occur in syphilis but are much more frequent in tuberculosis. The granulation tissue ultimately becomes fibrotic, and delicate elastic fibrils are formed. The elastic lamella and stripe remain unaltered throughout the process; this enables the condition to be recognized easily in sections stained by a specific method for demonstrating elastic.

The thickening of the intima by inflammatory granulation tissue differs

conspicuously from intimal hypertrophy. In intimal hypertrophy musculo-elastic and hyperplastic layers are formed, in which muscle fibres and lines of stout elastic fibres are arranged regularly. The regular arrangement is recognizable even when the hypertrophied intima has undergone degeneration. In intimal inflammation the thickening consists of irregularly arranged fibroblasts; when elastic fibres appear they are delicate and arranged irregularly. An elastic lamella may ultimately appear round the narrowed lumen, and a zone of muscularis may develop outside this; even when this occurs the appearance is unlike that of hypertrophy. Jores, 1903 (2), drew attention to these differences in appearance. By the term 'endarteritis fibrosa' he summarized the characteristics of inflammation of the intima.

The inflammation of the media and adventitia which accompanies the endarteritis conforms in type to the inflammation caused in other tissues by the particular infecting organism. In syphilis the adventitia and media are usually greatly infiltrated, and frequently necrosed. When necrosis is present, then, as in intense syphilitic reactions in other tissues, neutrophil leucocytes are abundant.

(iii) *Small arterioles.* In syphilitic arteritis of the smallest arterioles, in which an elastic lamella cannot be recognized, it is not possible to distinguish the reactions in the adventitia, media, and intima. The lumen becomes narrowed by infiltration and fibroblastic proliferation throughout the whole wall. It is further narrowed by swelling, proliferation, and desquamation of the endothelium. These changes are conspicuous in the small vessels in primary chancres.

Macroscopic Appearances of Arteritis of the Small Arteries.

The macroscopic appearances are most conspicuous in the cerebral arteries, especially those of the base. In most cases the artery shows externally a fusiform white thickening, and feels solid; on transverse section the cut surface consists of a firm grey tissue, in the centre of which there may be a minute red point indicating the lumen. In rare cases the artery is not thickened, but forms a somewhat contracted solid cord.

Presence of Spirochaetes in Muscular Arteries.

Spirochaetae pallidae were demonstrated by Levaditi's method in arteritis of the arteries of the base of the brain in syphilitic meningitis by Benda, 1906 (19); the patient was a male, aged 43. Strasmann, 1910 (20), published a most interesting case of meningo-encephalo-myelitis in which numerous spirochaetes were found, not only in the meninges, especially in the walls of the vessels, but also in the adventitial sheaths and walls of the vessels within the spinal cord and brain, and in the parenchyma surrounding these vessels; the patient was a male, aged 26, who had had a chancre one year and nine months before death.

Spirochaetes are found more frequently in the walls of arterioles in chancres. They are almost constantly present in the walls of arteries in syphilitic lesions of the organs of infants under nine months of age.

PART V.

ARTERIOSCLEROSIS.

'Arteriosclerosis' (σκληρός—hard) (5) means 'arterial hardening'. The term has been employed to denote hardenings of different kinds.

1. It has been applied to *hypertrophied* arteries, especially when these arteries are actively contracted. This form of arteriosclerosis is the essential arterial change in high blood-pressure. In the radial artery the degree of hardening may be found on palpation at different times to vary; the artery feels hardest when it is smallest. This proves that the hardening is due to physiological activity and not to degeneration. In this form of arteriosclerosis the resistance to expansion is increased; the elastic recoil is, probably, also increased.

2. In *atheroma*, when severe, and especially when calcareous, the artery is hardened. The resistance to expansion is increased, whilst the elastic recoil is decreased. Even in early atheroma, according to the experiments of Strasburger, 1907 (21), the resistance to expansion is increased. Marchand (22) has given the name 'Atherosclerosis' to hardening of the arteries caused by atheroma. A similar hardening of arteries is caused by the modification of atheroma described under the heading 'intimal fibrosis' (p. 209).

3. *Medial degeneration* also causes arteriosclerosis. This form of hardening is very obvious in peripheral arteries which are affected by Mönckeberg's degeneration. The radial artery may feel like a pipe-stem, and crackle beneath the finger on palpation. When degeneration without calcification leads to disappearance of the muscular fibres, or of both muscular and elastic fibres, the media becomes fibrous. The arterial wall is then harder, through loss of elasticity. The resistance to expansion may decrease so that diffuse or focal aneurysmal dilatation occurs.

The relation between the sclerosis caused by intimal and medial degenerations is given in Part II (p. 212), in the discussion on the correlation of the two forms of degeneration. As regards the relation between the sclerosis caused by these degenerations and sclerosis caused by hypertrophy:—Intimal hypertrophy in cases in which the blood-pressure is not abnormally high is associated with medial degeneration; the hypertrophied intima usually, but not invariably, becomes atheromatous or undergoes the less obvious form of degeneration, 'intimal fibrosis'. Medial and intimal hypertrophy in cases of high blood-

pressure are very apt to become complicated by medial and intimal degenerations.

4. *Amyloid infiltration* doubtless leads to a sclerosis of the affected arteries, particularly arterioles.

5. A fifth form of arterial hardening results from *inflammation*. The elastic recoil is decreased; the resistance to expansion may be increased or decreased.

General Arteriosclerosis.

Arterial hypertrophy in cases of general high blood-pressure is present throughout the greater circulation. It is, therefore, a general arteriosclerosis. The arterioscleroses caused by intimal and, especially, medial degenerations may also be so widespread as to merit the term general.

The scleroses caused by amyloid infiltration and by inflammations are focal; they cannot be included among general arterioscleroses.

Syphilitic infection may lead to focal arteriosclerosis by causing either inflammation or amyloid infiltration of arteries. I have found no evidence that syphilitic infection leads to any of the forms of general arteriosclerosis (*vide* Part I, pp. 204-6, and Part II, pp. 209 and 211).

PART VI.

ANEURYSM AND DIRECT RUPTURE.

The term 'aneurysm' includes any dilatation (*ἀνεύρω*, 'widen, dilate' (5)) of an artery. A general dilatation of an artery is called a *diffuse aneurysm*; when the artery is also tortuous the condition is known as *cirroid aneurysm*. Focal dilatations constitute *circumscribed aneurysms*; these are specified, according to their shape, or their size, as *fusiform*, *saccular*, *miliary*, and the like. Aneurysms are also classified according to their structure: (1) *True aneurysms* are dilatations which are bounded by the coats of the artery. (2) *False aneurysms* are cavities which communicate with the lumen of an artery, but are bounded by tissues external to the wall of the artery. (3) In *dissecting aneurysms* blood has passed from the lumen into the wall of the artery, and has separated one coat from another. (4) In a fourth group of aneurysms the lumen of an artery is connected with that of a vein. There are three varieties in this group—*aneurysmal varix*, *varicose aneurysm*, and *arterio-venous aneurysm*. A true aneurysm frequently ruptures and gives rise secondarily to a false aneurysm; the resulting structure is a *mixed aneurysm*.

In this paper all false aneurysms in which there is evidence of a primary dilatation, that is to say all mixed aneurysms, will be referred to as true. The

term *aneurysm* without any qualification will denote a true aneurysm. The term *direct rupture* will be employed to denote a rupture which has not been preceded by aneurysm. False aneurysms will, therefore, be included among 'direct ruptures'. Dissecting aneurysms will be treated as a special form of direct rupture.

Aneurysms may be congenital or acquired. Acquired aneurysms may be caused by (1) *trauma*, (2) *peptic digestion*, (3) *inflammations*, and (4) *degenerations*; (5) *loss of support* is in some cases an important contributory factor. All these conditions may also give rise to direct rupture. Vascular hypertrophy is not a cause of aneurysm or rupture, but (6) the *heightened blood pressure*, which is indicated by cardiovascular hypertrophy, is a most important contributory factor. Other things being equal, aneurysm and rupture are much more likely to occur when the blood-pressure is abnormally high. Further, as has been emphasized above, continued elevation of the blood-pressure leads to arterial degeneration.

I propose to treat in detail only such aneurysms or direct ruptures as result from the conditions which were described in Parts II and IV under the headings of degeneration and inflammation. Certain aneurysms and ruptures in the formation of which a congenital or a developmental abnormality in structure appears to play a part will also be discussed. For the sake of completeness a few words may first be said concerning aneurysm and rupture due to other causes.

Trauma from without is a rare cause of true aneurysm. A special mode of formation of aneurysm by trauma is described in the text-books, and is said to occur in the small arteries, especially the cerebral arteries. The aneurysm follows laceration or pressure atrophy of the inner coats of the artery by emboli which have broken off from calcareous atheromatous ulcers or calcified thrombi. The acceptance of this mode of aneurysmal formation appears to depend upon the authority of Ponfick, 1873 (23). Ponfick described seven cases of 'recurring verrucose endocarditis' in which there were mixed and false aneurysms of the cerebral, splenic, and superior mesenteric arteries. He showed that the aneurysms were clearly due to emboli; he was, thus, the first to describe embolic aneurysms. In his first and some of his other cases the vegetations and emboli were partly impregnated with calcium. In a long argument he attributed the weakening, or perforation, of the arterial wall to purely mechanical influences, whether the emboli were calcareous or not. The detailed descriptions of the organs, however, show that all seven cases were cases of progressive malignant endocarditis. Ponfick's failure to recognize the infective nature of the vegetations and emboli in such cases is emphasized by his quoting, as proofs of the correctness of his mechanical theory, both the formation of ulcerations of the wall of the ventricles beneath or in intermittent contact with vegetations, and the formation of aneurysms of valves. Ponfick's paper does not prove that traumatic aneurysms are caused by simple, calcareous emboli. Theoretically, aneurysms might well be caused in this way, but I know of no evidence that

they are. It need hardly be mentioned that rupture of arteries is frequently caused by traumatic incision or laceration. We have had instances of transverse rupture of the thoracic or abdominal aorta in cases of crushing of the chest or abdomen. In a case in 1913 fatal haemorrhage followed perforation of the aorta by a fish-bone embedded in the oesophagus.

Peptic erosion frequently leads to the formation of aneurysm in arteries which lie in the base of peptic ulcers. The aneurysms are often multiple. They are found in the base of chronic progressive ulcers, healing ulcers or erosions, and, occasionally, in ulcers or erosions which have completely healed. In the latter case they are seen as nodules projecting from a scar, and they are liable to rupture in consequence of renewed erosion. Loss of support by the surrounding tissues appears to play an important part in the formation of peptic aneurysms. Direct rupture is also frequently caused by digestive erosion of arteries in the base of peptic ulcers.

The conditions of *aneurysmal varix* and *varicose aneurysm* are usually the result of puncture wounds; they have become rare since operative venous puncture has ceased to be a panacea.

Arterio-venous aneurysm is caused by the rupture of an aneurysm into a vein. In the years 1908 to 1913, aneurysms due to syphilitic aortitis ruptured into the superior vena cava in two cases, and into the left innominate vein in one case. In this connexion it may be mentioned that rupture into the pulmonary artery occurred in two cases.

In discussing the parts played by inflammation, degeneration, and cardiovascular hypertrophy in the causation of aneurysm or direct rupture, it is advisable to treat separately (A) the large elastic arteries, and (B) the muscular and small elastic arteries. The small elastic arteries are represented by the branches of the pulmonary arteries.

A. LARGE ELASTIC ARTERIES.

(a) TRUE ANEURYSM.

I. *Inflammation, Syphilitic.*

1. *Aorta.* The formation of shallow sulci and pits, sometimes confined to the surface of intimal thickenings, or of diffuse aneurysmal dilatation, or of circumscribed, usually saccular, aneurysms, is almost invariably found when the aorta is the seat of syphilitic inflammation. Syphilitic inflammation is much the commonest cause of aneurysm of the aorta, and aneurysms of the aorta due to syphilis are the commonest form of all aneurysms in the body.

Shallow sulci and pits, or diffuse or saccular aneurysms, were found in all the 175 cases of syphilitic aortitis in the years 1908 to 1913. In fifty-four of these cases, i. e. in 30.8 per cent., there were sixty-four aneurysms giving clinical manifestations, including aneurysmal stretching of the commissure.

The sites of these aneurysms were as follows :

Arch of aorta	22	Abdominal aorta	2
Descending thoracic aorta	14	Commissure to termination of arch	1
Commissure	12	Commissure to termination of transverse arch	1
Ascending thoracic aorta	8	Ascending thoracic and arch	1
Junction of thoracic and abdominal	2	Arch and descending thoracic	1

2. *Other large elastic arteries.* Syphilitic inflammation is the commonest cause of aneurysm in the other large elastic arteries. The branches of the aorta are most commonly affected, the site of election being at, or close to, their origin. Such aneurysms are, however, much rarer than aortic aneurysms.

Aneurysmal pitting or pouching was present in all forty-three examples of syphilitic arteritis of the large elastic arteries during the years 1908 to 1913 (*vide* Table III, Part IV, p. 222), with the exception of arteritis affecting the secondary branch of the pulmonary artery.

Aneurysms giving clinical manifestations were present in five, i. e. 11.6 per cent. of the forty-three cases. Their sites were : innominate artery, three ; right common carotid, one ; left subclavian, one.

II. *Inflammation, Tuberculous.*

Inasmuch as tuberculous infection tends to cause a chronic sclerotic reaction, aneurysm is liable to occur in the aorta or other large elastic arteries when they are infected. Tuberculous inflammation of the large elastic arteries is, however, extremely rare.

In the years 1909 to 1913 there was only one case of tuberculous arteritis of a large elastic artery, namely, the aorta. In this case aneurysmal pitting and a large saccular aneurysm had resulted (*vide* Part IV, p. 218).

III. *Inflammation, Non-granulomatous.*

Non-granulomatous inflammation of the *aorta* is more acute and more rapidly destructive than tuberculous or syphilitic inflammation. Aneurysms, however, frequently result. In the formation of these aneurysms part of the wall of the aorta is often destroyed completely ; thus when the infection has spread from the intima, there is frequently ulceration of the intima and a portion of the media. The aneurysm is then not so pure a dilatation of the wall of the vessel as an aneurysm in syphilis. Aneurysms of the aorta caused by non-granulomatous inflammation are very rare in comparison to those caused by syphilis, because syphilitic infection is so much more common.

In the *other large elastic arteries* aneurysms caused by non-granulomatous inflammations are even rarer. These arteries are usually infected by spread from surrounding abscess or cellulitis, and direct rupture occurs more frequently than aneurysm.

In four of the five cases of non-granulomatous *aortitis* in the years 1908 to 1913, small saccular aneurysms had been formed (*vide* Cases 1 to 4, p. 217, Part IV). In these years there was one other case in which a small aneurysmal depression, in the ascending aorta, may have been the result of non-granulomatous inflammation. Microscopic examination showed that the depression corresponded to an area of completely healed *aortitis*. In the absence of active reaction it was impossible to determine the nature of the infection. The Wassermann test, applied *post mortem*, was negative; this does not, however, exclude healed syphilitic *aortitis*.

In the four cases in which *other large elastic arteries* were affected by non-granulomatous inflammation in 1908 to 1913 (*vide* Part IV, p. 218), rupture occurred without the formation of aneurysms. In one necropsy in 1907 an aneurysm of the external carotid, close to its origin, resulted from direct inward spread of purulent inflammation from an abscess of the neck.

IV. *Degeneration, Intimal.*

Degeneration confined to the intima does not cause true aneurysm. Before the wall of the artery stretches the media must be affected. The aneurysms caused by degenerations are due to medial degeneration.

V. *Degeneration, Medial.*

1. *Aorta.* Fatty or mucous degeneration, usually accompanied by calcareous impregnation, leads very frequently to *diffuse dilatation* of the aorta, especially of the thoracic aorta. The medial degeneration is accompanied by intimal hypertrophy and a varying degree of atheroma or 'intimal fibrosis'. Such diffuse dilatation, associated with intimal thickening, is easily recognized in almost every male over the age of fifty. There is frequently very little intimal degeneration visible to the naked eye. In rare cases the diffuse dilatation is very great. In these cases calcareous atheroma may be so extensive that the term 'pavement aorta' is appropriate. Continued high blood-pressure is an important factor in the formation of great, diffuse dilatation.

Similar degenerations of the media may lead to *small pitted and wrinkled areas* which resemble lesions caused by syphilitic *aortitis*. The majority of these are found in old subjects, or in subjects in whom the blood-pressure has been abnormally high. They are areas in which a general degeneration of the media is of maximal intensity. Similar lesions, due to medial degeneration, may occur in syphilitic subjects. In one or two cases the degeneration has then appeared histologically to be of exceptional severity. I have not, however, been able to

detect any special characteristic in the nature of the degeneration. The total number which I have observed of cases of pits and pouches due to medial degeneration does not suffice to enable a decision to be made by statistics as to whether infection by syphilis is more than a coincidence. Occasionally, a small wrinkled and dilated area, usually pearly white in colour, is found in the aorta of young subjects, when there is no evidence of syphilis or of abnormally high blood-pressure and when there is little degeneration in the remainder of the media. These areas have been situated in, and immediately above or below, the commissure. The focal medial degeneration in these cases appears, from microscopic examination, to originate in rupture of elastic fibres. The muscular fibres of the media are thus exposed to excessive pressure and consequently to mechanical injury or deprivation of nutrition. The initial rupture is doubtless due to pressure. This view is supported by the observation that these pits occur at the site of election of complete ruptures which are independent of inflammation or degeneration (*vide infra*, p. 241). The neighbourhood of the commissure is specially exposed and susceptible to pressure. It is the site of the greatest lateral pressure in the aorta. The sinuses of Valsalva are structurally weak, because in them the elastic and muscular media rapidly narrows towards the base of the aortic cusps. The exposure of the root of the aorta to the maximal pressure explains why this site should also be so frequently affected in the group of cases in which pitting is associated with general medial degeneration.

In the years 1908 to 1913 *very marked, diffuse dilatation*, associated with severe atheroma, was present in four cases of medial degeneration. In two cases the whole thoracic aorta was affected; in two the ascending aorta and arch were affected. In three cases cardiovascular hypertrophy was present, the subjects being males aged 56, 55, and 48. In the fourth case there was brown atrophy of the heart, the subject being a male, aged 46, who died of cancerous cachexia.

During these years *small pitted or wrinkled areas*, resembling aortitic lesions, were present in eighteen cases. In ten of these, excessive blood-pressure was demonstrated at necropsy by cardiovascular hypertrophy. The sexes and ages of these ten subjects, and the sites of the lesions, were as follows: M., 71, ascending aorta; M., 68, ascending aorta; M., 66, commencement of descending thoracic aorta; F., 63, arch of aorta; F., 60, abdominal aorta; M., 59, commencement of descending thoracic aorta; F., 57, aortic commissure; M., 51, immediately above commissure; M., 49, arch and left posterior sinus of Valsalva; F., 37, arch of aorta.

In the remaining eight cases there was no evidence of excessive blood-pressure. The sexes and ages of the subjects, and the sites of the lesions, were as follows: M., 73, commencement of descending thoracic aorta; M., 68, immediately above commissure; M., 67, immediately above commissure; F., 53, descending thoracic aorta; M., 50, right posterior sinus of Valsalva; M., 46, in and above commissure; M., 46, commissure and pouches of Valsalva, and descending thoracic aorta; F., 27, in and above commissure. The man aged 53 had gummatous ulceration of the scalp and skull. The man aged 50 had fibrosis of both testicles, obliteration of both tunicae vaginales, and a scar on the penis. The man aged 46, mentioned seventh in the above list, had fibrosis of the right testicle and obliteration of both tunicae vaginales; he gave a history of having contracted syphilis and gonorrhoea at a date twenty-five years before his death, but the Wassermann test applied to his serum twenty-three days before death

proved negative. The woman aged 27 affords an example of severe focal degeneration which was apparently the sequel of rupture of elastic fibres. Her death was due to toxæmia of pregnancy.

2. In the *other large elastic arteries* slight diffuse dilatation frequently results from medial degeneration. Focal aneurysmal dilatation is very rare. There is frequently an exaggeration of the normal dilatation at the site of the origin of the internal and external carotid arteries. In microscopic sections, however, this has appeared to be due to a congenital deficiency in muscular fibres at this arterial bifurcation, and not to a degeneration.

In 1908 to 1913 there was no example of focal aneurysmal dilatation, due to medial degeneration, in the large elastic arteries other than the aorta.

(b) DIRECT RUPTURE AND DISSECTING ANEURYSM.

I. *Inflammation, Syphilitic.*

Rupture of the aorta or other large elastic artery due to syphilitic inflammation, before the formation of an aneurysm, is very rare. This might be expected, because syphilitic arteritis is characteristically a chronic process. In the rare cases of acute syphilitic inflammation rupture may occur.

In 7,924 necropsies in the years 1907 to 1913 there was no instance of syphilitic arteritis of a large elastic artery leading to dissecting aneurysm or to rupture, before the formation of a true aneurysm.

II. *Inflammation, Tuberculous.*

Tuberculous inflammation may lead to rupture of the aorta when only slight dilatation has occurred. Thus Kamen, 1895 (24), described a case in which tuberculous infiltration of the ascending aorta, over an adherent caseous lymphatic gland, had been followed by rupture of the intima, a dissecting aneurysm, and, finally, rupture of the media and adventitia. The affected portion of the aorta was only slightly widened.

III. *Inflammation, Non-granulomatous.*

1. *Aorta.* The non-granulomatous inflammations of the aorta usually occur in cases of septicaemia and pyaemia, particularly in cases of malignant endocarditis. The various infecting organisms cause a reaction which, if intense, is definitely purulent. The liability to direct rupture is, therefore, much greater than in syphilitic or tuberculous aortitis. It has been pointed out (p. 236) that when aneurysms are formed a portion of the wall of the aorta is frequently eroded. This is especially liable to occur when the infection is from the intima in cases of malignant endocarditis; ulcerative endoaortitis may then play a part

in the formation of the aneurysm. The reason why direct rupture is not more common is to be found, perhaps, in the frequency with which the infection occurs in progressive malignant endocarditis; infection in progressive endocarditis being, in general, characterized by relative mildness and by little tendency to the formation of true abscesses.

Rupture occurred in only one of the five cases of non-granulomatous aortitis in 1908 to 1913 (*vide* Part IV, p. 217); the rupture had been preceded by the formation of an aneurysm. In this case (No. 4) microscopic examination showed that the floor of the proximal portion of the aneurysm was formed by granulation tissue containing a few fragments of medial elastic; at the distal extremity an extensive purulent infiltration passed through the whole wall of the aorta and had caused rupture. In Case 2 also there was an acute purulent extension at one extremity of the aneurysm; here the pus dissected the intima from the media and also made a horizontal split in the centre of the media, for a short distance. In Case 4 septicaemia had existed for seventeen weeks. Two attempts to cultivate bacteria from the blood, during life, failed. Cases 1, 2, and 3 were examples of progressive malignant endocarditis. In Case 5 the septicaemia was of a very chronic and mild type. The inflammation was almost confined to the intima; infiltration of the media and adventitia, with neutrophil leucocytes, was slight. Neither aneurysm nor rupture had resulted.

2. *Other large elastic arteries.* These arteries are especially liable to rupture without the formation of an aneurysm when they are infected by spread of inflammation from a surrounding abscess or cellulitis (*vide* cases quoted, p. 237).

IV and V. *Degenerations, Intimal and Medial.*

Intimal or medial degenerations may lead to dissecting aneurysm. They are much more often than inflammations the cause of such aneurysms.

Dissecting aneurysms may originate in atheromatous ulcers. If there is relatively little medial degeneration and the blood-pressure is not abnormally high, the dissecting aneurysms are small; the dissection seldom extends for more than one centimetre round the margin of the ulcer. Such *small dissecting aneurysms* occur very often in the aorta, especially in the abdominal aorta. They are frequently indicated at post-mortem examination by a dark blue zone of altered blood beneath the intima at the edge of an ulcer. In the other large elastic arteries small dissecting aneurysms are much rarer, because in these arteries atheromatous ulceration is much less common.

In the causation of *extensive dissecting aneurysm* medial degeneration and abnormally high blood-pressure appear to be more important factors than intimal degeneration. The incidence of such aneurysms corresponds to the severity of medial rather than of intimal degeneration. The dissection frequently originates in an area in which there is no atheromatous ulceration. It may, indeed, arise in a split in a portion of intima in which there is little degeneration; the splitting of the intima in such a case is presumably the result of excessive expansion of the subjacent degenerate media. Extensive dissecting aneurysm is rare in the aorta, and is very rare in the other large elastic arteries.

In extensive dissecting aneurysm the dissection separates in places the intima from the media, in places the media from the adventitia. The condition may sometimes be recognized clinically by the association of an actively beating heart with a feeble arterial pulse. Extensive dissection does not necessarily cause death. The channel formed by dissection may become lined so that the original aorta forms a vessel within a newly made vessel.

The following cases of extensive dissecting aneurysm of *the aorta*, due to degeneration, occurred during the years 1908 to 1913 :

1. M., aged 70. Arising in an atheromatous ulcer in the abdominal aorta and extending for 5 cm. Moderate atheroma, and considerable medial degeneration of aorta. Moderate cardiovascular hypertrophy.

2. M., aged 57. Arising in the abdominal aorta, and dissecting the terminal 7 cm. of the aorta and both common iliac arteries. Severe atheroma and severe medial degeneration. No atheromatous ulceration. Ruptured aneurysms in an epiploic and lumbar artery. Very great cardiovascular hypertrophy.

3. M., aged 70. Extending from origin of aorta to the lower border of the right crus of the diaphragm. Rupture into the pericardial sac. Severe atheroma and severe medial degeneration. Extensive atheromatous ulceration. No evidence of cardiovascular hypertrophy.

4. M., aged 59 (in list p. 238). Rupture in intima, 1 cm. in diameter, immediately above a small pitted patch at the commencement of the descending thoracic aorta. Dissection of descending thoracic and abdominal aorta, and right common iliac artery. Dissected cavity partially lined. Moderate atheroma and severe medial degeneration. Great cardiovascular hypertrophy.

5. M., aged 41. Rupture in arch immediately below origin of left subclavian artery. Dissection extending from left subclavian artery to bifurcation of aorta. Considerable atheroma and medial calcification. No atheromatous ulceration. Very great cardiovascular hypertrophy.

In these years there were no examples of extensive dissecting aneurysms arising in the *other large elastic arteries*.

VI. *Developmental Deficiency, Relative or Actual.*

The coats of the aorta occasionally rupture and give rise to dissecting aneurysm when there is no trace of inflammation, when intimal and medial degeneration are slight, and when there is no evidence of persistently high blood-pressure. The only possible explanation of rupture in these cases is that the development of the aorta has been insufficient. Such rupture occurs in man most frequently in the sinuses of Valsalva and the lower portion of the ascending aorta. In animals, also, rupture of the aorta occurs most frequently in the sinuses of Valsalva (Casper, 1896 (25)). It has already been suggested that the neighbourhood of the commissure is not only exposed to the greatest lateral pressure, but is structurally weak. The development of the aorta in such cases may be relatively or actually insufficient. That is, either an aortic wall of average strength has ruptured on exposure to a sudden strain of exceptional severity, or the wall has not attained the normal strength, and has therefore been unable to withstand a strain of average intensity. In the two cases

outlined beneath, which occurred in 1908 to 1913, the evidence is against the assumption that rupture followed exceptionally severe strain upon vessels of normal development and strength. First, there was, according to the histories, no violent exertion at the time of rupture. Secondly, the whole ascending aorta in both cases was slightly dilated and abnormally thin; a condition which was evidently chronic. This association of diffuse dilatation with thinning of the aortic wall is very exceptional. Slight diffuse dilatation of the aorta is very common, but it is associated with an intimal hypertrophy which is sufficiently great to cause a thickening of the wall recognizable by the naked eye (*vide* p. 237). The microscope showed that the development of the intima in the two cases under discussion was exceptionally slight. The dilatation and rupture were probably due to failure of the intima to undergo the hypertrophy which in a normal individual would have compensated such medial degeneration as was present. In these two cases, therefore, rupture appears to have occurred because the development of the aorta was actually imperfect; rupture was the consequence of hypoplasia.

1. F., aged 42. Transverse rupture, 4 cm. long, within the two posterior pouches of Valsalva immediately below the commissure. Dissection extending throughout the whole aorta and for 2.5 cm. along the left common iliac artery. Pouches of Valsalva thin and dilated; ascending aorta thin and slightly dilated. Very slight atheroma of thoracic aorta; a few small fatty flecks in commissure, one fatty plaque at site of obliterated ductus arteriosus. Numerous fatty plaques and streaks in abdominal aorta. Slight medial degeneration on microscopic examination. Very little development of intima of ascending thoracic aorta. No cardiovascular hypertrophy. No history of muscular exertion at time of rupture.

2. F., aged 50. Complete transverse rupture across the aorta, 7.5 cm. above the commissure. Dissection extending throughout the whole aorta and the right common iliac artery. Ascending aorta thin, smooth, and slightly dilated. Slight atheroma; a fatty streak in commissure; scattered fatty plateaux in descending arch, descending thoracic aorta and abdominal aorta. Slight degeneration in centre of media on microscopic examination. Very little development of intima of ascending thoracic aorta. No cardiovascular hypertrophy. Rupture occurred 'whilst patient was buying fish'.

B. MUSCULAR AND SMALL ELASTIC ARTERIES.

(a) TRUE ANEURYSM.

I. *Inflammation, Syphilitic.*

It has been pointed out in Part IV, p. 230, that when the smaller muscular and elastic arteries are the seat of syphilitic inflammation endarteritis is usually a marked feature, the lumen becoming almost obliterated. It is clear that in such a condition aneurysmal dilatation is excluded. In some cases of intense inflammation with necrosis the adventitia and media become greatly weakened before the intima has greatly thickened; in such cases aneurysmal

dilatation might occur, but in my experience such intense inflammation has led to rupture or false aneurysm and not to true aneurysm. In the largest muscular arteries, on the other hand, syphilitic inflammation tends to weaken the wall, without occlusion of the lumen by granulomatous intimal thickening. In these arteries, therefore, as in the large elastic arteries, aneurysmal dilatation is very liable to occur. Syphilitic inflammation of the large muscular arteries is rare, and is commonest in the branches of the aorta close to their origin.

In 1908 to 1913 there were six examples of syphilitic arteritis of large muscular arteries: coeliac axis, 3; superior mesenteric artery, 2; splenic artery, 1 (p. 230). In all these six examples there was aneurysmal pouching. In the case of inflammation of the splenic artery and in one example of arteritis of the coeliac axis the aneurysms gave clinical manifestations. The splenic aneurysm ruptured into the stomach.

II. *Inflammation, Tuberculous.*

In the majority of cases of arteritis in tuberculous lesions the lumen of the artery becomes greatly narrowed or closed by endarteritis, and there is no aneurysmal dilatation. Tuberculosis infiltrating the media of the large muscular arteries can lead to aneurysm, just as it does in the large elastic arteries. This condition is, however, extremely rare.

In chronic pulmonary tuberculosis, with cavitation, aneurysms of the pulmonary branches are common. Here the loss of support by surrounding tissue which results from the cavitation appears to be a more important factor than tuberculosis of the artery. The aneurysms project into cavities. Erosion of the arterial wall by tuberculosis, or by secondary infection, does, however, play a part. Fatal haemorrhage in chronic phthisis is almost invariably due to rupture of such an aneurysm.

In 1908 to 1913 the only aneurysms associated with tuberculosis of muscular and small elastic arteries were found on pulmonary arteries in chronic tuberculous cavities in the lungs. In nine examples the aneurysm was ruptured and had led to fatal haemorrhage. In one case an unruptured aneurysm was found. Doubtless more numerous aneurysms would have been found if it had been possible to make a complete investigation of all lungs in which there were chronic vomicae.

III. *Inflammation, Non-granulomatous.*

Aneurysms of the muscular arteries frequently result from infection by bacteria which cause acute inflammations. The arteries are most commonly infected by impaction of emboli in their lumina. The aneurysms are usually a mixture of true aneurysmal dilatation and false aneurysm. Rupture of the covering of the false aneurysm is very liable to follow.

Aneurysms due to infective embolism are found most frequently in the cerebral arteries; the superior mesenteric artery is the second site of election. In our records they have occurred most frequently in cases of progressive malignant endocarditis.

TABLE V.

Aneurysms in Muscular Arteries caused by Infective Emboli, 1907 to 1913.

Number of Cases.	Right mid. cerebral.	Left mid. cerebral.	Branch on vertex right mid. cerebral.	Branch on vertex left mid. cerebral.	Right anterior cerebral.	Left anterior cerebral.	Left intracranial carotid.	Bifurcation of basilar.	Superior mesenteric.	Coeliac axis.	Splenic.	Intrahepatic hepatic.	Left renal.	Left prof. femoris.	Right brachial.	Left brachial.	Posterior branch of coronary.	Branch of deep epigastric.
4	4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—
1	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	—	—	1	—	—	—	—	—	—	—	—	—	1	—	—	—	—
1	—	—	—	—	—	—	1	—	—	1	—	—	—	—	—	—	—	—
1	—	1	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—
1	—	1	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—
1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
*1	—	—	—	—	—	—	—	—	1	—	—	—	—	—	1	—	—	—
*1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—
*1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—
2	—	—	—	—	—	—	—	—	2	—	—	—	—	—	—	—	—	—
*3	—	—	—	—	—	—	—	—	3	—	—	—	—	—	—	—	—	—
*1	—	—	—	—	—	—	—	—	1	—	—	1	—	—	—	—	—	—
2	—	—	—	—	—	—	—	—	—	—	2	—	—	—	—	—	—	—
25	4	4	1	1	2	1	1	1	8	1	2	1	1	1	1	1	1	1

The sites of aneurysms caused by *infective embolism* during the years 1907 to 1913 are given in Table V. In this table there are 33 aneurysms which occurred in 25 cases; 15 aneurysms were found in cerebral vessels, 18 in other vessels. In 7 cases (marked with an asterisk) in which vessels other than the cerebrals were affected, examination of the head was not permitted. In these 7 cases there were 9 aneurysms. If these partial examinations are omitted the proportion of aneurysms in the cerebral arteries to those in other arteries is 15 to 9.

Of the total 33 aneurysms, 20 caused extensive haemorrhage by rupture. In 17 of the 25 cases there was progressive malignant endocarditis. In 2 cases there was a more acute malignant endocarditis. In 3 cases there was puerperal pyaemia. In the remaining 3 cases there was a chronic pyaemia; in one of these the pyaemia complicated a retropharyngeal abscess, in the other two the seat of primary infection was not ascertained.

In the same period, 1907 to 1913, three aneurysms were caused in muscular arteries by *infection from without*. The arteries affected were: the left deep epigastric, the right internal iliac, and the right uterine artery.

IV. Degeneration, Medial.

Diffuse dilatation resulting from medial degeneration is frequently found in the muscular arteries. It occurs most frequently in the cerebral and splenic arteries. The dilated splenic arteries are frequently tortuous, forming 'cirroid

aneurysms'. In the cerebral arteries diffuse dilatation is often found when there is no macroscopic atheroma. It is usually associated with cardiovascular hypertrophy. The cerebral arteries in cases associated with cardiovascular hypertrophy often form a sharp contrast to the radial and femoral arteries, the medial hypertrophy in the radial and femoral being recognized readily by the naked eye, whilst the cerebral arteries appear large but thin.

Slight focal dilatation may be present at the site of atheromatous plaques. This is almost constant in atheroma of the cerebral arteries, but is less common in other muscular arteries. Microscopic examination of atheromatous plaques in the cerebral arteries reveals extreme degeneration and thinning of the subjacent media. When medial degeneration leads to a diffuse dilatation of the cerebral arteries unaccompanied by macroscopic atheroma the medial degeneration is less severe. Macroscopic atheroma may, therefore, be taken as an indication of the degree of medial degeneration in the cerebral arteries.

Saccular aneurysms, due to medial degeneration independent of inflammation, are found much more commonly on the cerebral arteries than on any other muscular arteries (compare Tables VI and VII). Such aneurysms are very rare upon the central branches of the cerebral arteries. In many cases of cerebral haemorrhage there appear to be miliary aneurysms upon central branches, but in all cases, with one exception, which I have examined, these have been found on microscopic examination to be false aneurysms, or portions of clot adherent to a vessel. The saccular aneurysms are situated usually upon an artery of the first order, less commonly upon a cortical branch of such an artery. They may be single or multiple. The great majority are on, or close to, the anterior portion of the circle of Willis. They almost invariably spring from the point of junction of two arteries, either a junction in the circle of Willis or the origin of a branch. A favourite position is the junction of the anterior communicating artery with an anterior cerebral. When the aneurysm is in this position it is buried between the mesial surfaces of the frontal lobes, where these lobes are not separated by arachnoid membrane. Rupture of aneurysms in this position, therefore, usually leads to erosion of one of the frontal lobes and final haemorrhage into the ventricles. In other positions rupture usually leads to subarachnoid haemorrhage only. The examples in Table VI varied in size from a pin-head to 3 cm. in diameter; the majority were of the size of a green pea.

In Table VI the sites of the aneurysms due to medial degeneration on the cerebral arteries during 1907 to 1913 are tabulated; in Table VII those present on other muscular arteries during the same period are enumerated. In both tables notes on the condition of the cardiovascular system are appended. In none of the cases of cerebral aneurysm was there evidence of active or healed endocarditis. There are 30 cases with aneurysms, due to medial degeneration, on cerebral arteries as opposed to 8 cases with similar aneurysms on other muscular arteries. During these years there were 7,924 examinations of the body; examination of the head was permitted in 5,432. Aneurysms due to medial degeneration were found, therefore, on the cerebral arteries in 0.55 per cent. of examinations of the brain, and on other muscular arteries in 0.10 per cent. of examinations of the body.

TABLE VI. *Saccular Aneurysms of Cerebral Arteries*

Sex.	Age.	Left intracranial carotid.	Origin of cortical branch from left carotid.	Junction of right carotid with posterior communicans.	Junction of left carotid with posterior communicans.	Junction of right carotid with right mid. cerebral.	Right mid. cerebral on base of brain.	Left mid. cerebral on base of brain.	Cortical branch 4 cm. from origin of right mid. cerebral.	Central branches of right mid. cerebral.	Junction of right anterior cerebral with anterior communicans.	Junction of left anterior cerebral with anterior communicans.
M	51	—	—	—	—	—	1 R	—	—	—	—	—
F	48	—	—	—	—	—	1	—	—	—	—	—
M	60	—	—	—	—	—	—	—	—	1, 1 R	—	—
F	49	—	—	1	—	—	—	—	—	—	—	1 R
M	49	—	—	—	—	—	—	—	—	—	—	1
F	44	—	—	—	—	—	—	—	—	—	—	1 R
M	86	—	—	—	—	—	1	—	—	—	—	—
M	75	—	—	—	—	—	—	—	—	—	—	1
M	50	—	—	—	—	—	—	—	—	—	—	—
M	55	—	—	—	—	—	1	—	—	—	1 R	—
M	53	—	—	—	—	—	—	—	—	—	—	1
F	46	—	—	—	—	—	—	—	—	—	—	—
F	72	—	—	—	—	—	—	1 R	—	—	—	—
F	67	—	—	—	—	—	—	—	—	—	—	—
F	60	—	—	—	—	—	1 R	—	—	—	—	—
M	53	—	—	—	—	—	—	—	—	—	—	1 R
M	51	—	—	—	—	—	—	—	—	—	—	1 R
F	49	—	—	—	—	—	—	—	—	—	—	—
F	48	—	—	—	—	—	1	—	—	—	—	—
M	47	—	—	—	—	1	—	—	—	—	—	—
F	43	—	—	—	—	—	—	1	—	—	—	—
F	42	—	—	—	—	—	—	—	—	—	—	—
M	41	—	—	—	—	—	—	—	—	—	1 R	—
F	40	—	—	—	—	—	—	—	—	—	—	—
M	36	1 R	—	—	—	—	—	—	—	—	—	—
F	36	—	—	—	1 R	—	2	—	—	—	—	—
M	28	—	1 R	—	—	—	—	—	—	—	—	—
M	22	—	—	—	—	—	—	—	1 R	—	—	—
M	19	—	—	—	1 R	—	—	—	—	—	—	—
M	40	—	—	—	—	1 R	—	—	—	—	—	—
30	Cases	1	1	1	2	2	8	2	1	2	2	7

du

Right anterior cerebral immediately beyond anterior communicans.

1 R

1

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—

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2

due to Medial Degeneration, 1907 to 1913.

Right anterior cerebral immediately beyond anterior communicans.	Left anterior cerebral immediately beyond anterior communicans.	Anterior communicans.	Junction of right posterior cerebral with posterior communicans.	Left anterior inferior cerebellar.	Macroscopic atheroma in aneurysm.	Macroscopic atheroma in cerebral arteries.	Diffuse dilatation of cerebral arteries.	General arterial degeneration throughout body.	Cardiovascular hypertrophy.
—	—	—	—	—	present	considerable	—	severe	very great
—	—	—	—	—	present	considerable	present	moderate	"
—	—	—	—	—	absent	severe	—	severe	great
—	—	—	—	—	absent	slight	present	moderate	"
—	—	—	—	—	absent	considerable	present	considerable	"
—	—	—	—	—	absent	considerable	—	moderate	"
—	—	—	—	—	absent	considerable	present	severe	considerable
1 R	—	—	—	—	present	severe	present	severe	"
—	—	—	—	—	absent	very slight	—	considerable	"
—	—	—	—	—	absent	absent	present	considerable	moderate
1	—	—	—	—	absent	slight	—	considerable	"
—	—	—	—	—	absent	slight	present	moderate	"
—	1 R	—	—	—	absent	—	—	considerable	slight
—	—	—	—	—	absent	considerable	present	severe	"
—	—	—	—	—	absent	absent	—	slight	absent
—	—	—	—	—	absent	slight	—	slight	"
—	—	1 R	—	—	absent	one fleck	absent	slight	"
—	—	—	—	—	absent	absent	absent	slight	"
—	—	—	—	—	absent	absent	absent	slight	"
—	—	—	—	—	absent	absent	absent	slight	"
—	—	—	—	1 R	absent	absent	—	moderate	"
—	—	—	—	—	absent	absent	absent	slight	"
—	—	—	—	—	absent	absent	—	slight	"
—	—	—	1 R	—	present	absent	—	very slight	"
—	—	—	—	—	present	absent	—	very slight	"
—	—	—	—	—	absent	absent	—	very slight	"
—	—	—	—	—	absent	absent	absent	very slight	"
—	—	—	—	—	absent	absent	—	very slight	"
—	—	—	—	—	absent	absent	absent	very slight	"
2	1	1	1	1	absent	absent	absent	examination alone per	of head mitted

Two minute aneurysms were situated, in one case, upon central cerebral branches. Of the remaining 33 all except one sprang from cerebral arteries of the first order; only 2 were connected with the posterior part of the circle of Willis. Of these 33 aneurysms, 15 sprang from the actual point of junction of arteries in the circle, 6 were close to such junctions, 10 arose from the point of origin of branches. In 2 no note was made upon the relation to points of junction or bifurcation.

In Tables VI and VII the letter 'R' indicates 'rupture' of the aneurysms. Rupture had occurred in 21 of the 35 aneurysms on cerebral arteries. In the case in which two aneurysms were found on central branches, one aneurysm had ruptured; the aneurysm on the cortical branch of the right middle cerebral had ruptured; 19 of the 32 aneurysms on cerebral arteries of the first order had ruptured.

Rupture had occurred in one of the 12 aneurysms, due to medial degeneration, on muscular arteries other than the cerebral.

Atheroma is seldom visible to the naked eye in these cerebral aneurysms. On microscopic examination there is a variable degree of thickening of the intima, and this intimal hypertrophy is usually degenerate. The media is extremely narrow and fibrous, elastic and muscular elements usually being entirely absent.

As can be seen in Table VI, in some cases there is evidence of cardiovascular hypertrophy, accompanied by a considerable degree of general arterial degeneration. In such cases there would appear to be an adequate explanation of the formation of the aneurysms. In many cases, however, there is no evidence of excessive blood-pressure, and the general arterial degeneration and the degeneration of the cerebrals are no greater than in the average subject of the same age. In this respect many of the cases of aneurysm contrast sharply with the cases of direct rupture of central cerebral arteries. Direct rupture is usually associated with evidence of much more excessive blood-pressure and greater arterial degeneration (compare Table IX). If, therefore, these cerebral aneurysms were entirely the result of excessive blood-pressure and arterial degeneration, they would precede and be more common than direct rupture. Comparison of Tables VI and VIII shows, however, that direct rupture is much more common. There appears, therefore, to be an additional factor in the formation of these cerebral aneurysms. This factor is, probably, an inherent weakness due to a congenital abnormality in the structure of the arteries at their points of junction. This conclusion is strengthened by our finding this year (1914) an aneurysm at the junction of the left anterior cerebral with the anterior communicating artery, in a child, aged 1 year and 7 months, who died of broncho-pneumonia complicating gastro-enteritis.

Saccular aneurysms, due to medial degeneration, of *muscular arteries other than cerebral* (Table VII), are usually associated with conspicuous vascular degeneration, and this is often accompanied by excessive blood-pressure. The splenic artery is most frequently affected. This might be expected, because the splenic artery very frequently shows great medial and intimal degeneration associated with diffuse dilatation and tortuosity. Aneurysms of the large

muscular arteries of the limbs are extremely rare. The popliteal space is a favourite site.

TABLE VII.

Saccular Aneurysm, due to Medial Degeneration, of Muscular Arteries other than Cerebrals, 1907 to 1913.

Sex.	Age.	Right thy-roid axis.	Splenic.	Epiploic.	Lumbar.	Macroscopic atheroma in aneurysm.	Macroscopic atheroma in affected artery.	Diffuse dilatation of affected artery.	General arterial degeneration.	Cardio-vascular hypertrophy.
M	57	—	—	1 R	1	absent	—	—	severe	very great
F	65	—	1	—	—	severe	severe	present	severe	great
M	55	1	—	—	—	absent	absent	present	considerable	"
F	69	—	2	—	—	severe	severe	present	severe	absent
F	64	—	3	—	—	severe	severe	present	considerable	"
F	62	—	2	—	—	severe	—	—	considerable	"
F	55	—	1	—	—	severe	severe focal	present	considerable	"
7 cases		1	9	1	1					

I have only had one opportunity of examining such aneurysms of the large muscular arteries of the limbs. The material was obtained from the surgical theatres. The aneurysms were multiple. The patient was a male, aged 76. The Wassermann test was negative. The blood-pressure in the brachial arteries was 115 millimetres of mercury.

The right leg and, nine months later, the left leg were amputated for gangrene of the feet. In the right popliteal artery there were two fusiform aneurysms separated by an isthmus; each measured 6 cm. in length and 4.4 cm. in greatest diameter. In the left popliteal artery two fusiform aneurysms were merged together, the total length being 13 cm. and the greatest breadth 5 cm. There were also: an aneurysm (2.5 by 3.5 cm.) in the left popliteal artery, 2 cm. below the above; a fusiform aneurysm (5 by 3 cm.) in the left posterior tibial; three saccular aneurysms (1 cm. in diameter) in the termination of the left superficial femoral. The arteries of the limbs showed severe fatty intimal degeneration and thinning of the media. On microscopic examination all the arteries showed severe degeneration and thinning of the media. In the degenerate media there were only a few small areas of impregnation by small granules of calcium. The hyperplastic layer of the intima was greatly hypertrophied, but the evidence of hypertrophy was, almost everywhere, obscured by extreme degeneration. Fatty atheromatous areas were very numerous, and gave rise to numerous dissecting aneurysms of the intima. There was more calcification in the intima than in the media, but the calcification was very slight. In the more severely affected areas there was vascularization of the media and intima; this was associated with infiltration by fibroblasts, lymphocytes, fat-granule cells, pigment-granule cells, and, in places, neutrophil leucocytes.

(b) DIRECT RUPTURE AND FALSE ANEURYSM.

I. *Inflammation, Syphilitic.*

Syphilitic inflammation of the muscular arteries, if intense, may lead to rupture with or without the formation of a dissecting aneurysm. Save in the smallest arterioles such an occurrence is rare.

In 1907 to 1913 there was one case of considerable haemorrhage due to dissecting aneurysm and rupture of the right middle cerebral artery, at the site of acute syphilitic arteritis.

II. *Inflammation, Tuberculous.*

Erosion of small arteries occurs in acute caseous tuberculosis; for instance, in caseous broncho-pneumonia. Severe haemorrhage caused by tuberculous erosion of larger arteries is rare, except in the case of arteries exposed within vomicae.

III. *Inflammation, Non-granulomatous.*

Muscular arteries and small elastic arteries may be eroded without the formation of aneurysms, by purulent infiltration from without, by infective embolism of vasa vasorum, or by infective embolism into the lumen. When arterioles are affected it is impossible to determine, without microscopical examination, whether the haemorrhage is caused by infective embolism or by toxic medial degeneration.

In 1907 to 1913 *infection from without* led to direct rupture of the following three large muscular arteries: left superficial femoral artery, left common femoral artery, radial artery. There were three cases of direct rupture of large cerebral arteries following *infective embolism*. In all three cases there was progressive malignant endocarditis. Ruptures of small cerebral arteries were present in six cases of malignant endocarditis, three of which were 'progressive', in one case of puerperal pyaemia, and one pyaemia of unknown origin. In these years, therefore, infective embolism caused in the cerebral vessels aneurysm, with or without secondary false aneurysm, more frequently than direct rupture (*vide* Table V).

TABLE VIII.

Site of Direct Rupture, due to Medial Degeneration, of Central Branches of Cerebral Arteries, 1907 to 1913.

Number of cases.	Right basal ganglia.	Left basal ganglia.	Pons.	Cerebellum.	Cerebral cortex.
22	22	—	—	—	—
1	1	—	—	—	1
15	—	15	—	—	—
6	6	6	—	—	—
1	1	1	—	—	1
3	3	3	3	—	—
6	6	—	6	—	—
4	—	4	4	—	—
10	—	—	10	—	—
2	—	—	—	2	—
1	—	—	1	1	—
1	—	—	1	1	1
72	39	29	25	4	3

TABLE IX.

Condition of Vascular System in Cases of Direct Rupture of Central Cerebral Arteries due to Medial Degeneration, 1907-13.

Sex.	Age.	Macroscopic atheroma of cerebral vessels.	General vascular degeneration.	Cardio-vascular hypertrophy.	Sex.	Age.	Macroscopic atheroma of cerebral vessels.	General arterial degeneration.	Cardio-vascular hypertrophy.
M	64	severe	severe	<i>very great</i>	M	50	severe	severe	<i>considerable</i>
M	61	severe	considerable	"	M	50	severe	severe	"
M	57	severe	considerable	"	M	47	very slight	slight	"
M	52	severe	severe	"	M	46	absent	moderate	"
M	48	severe	considerable	"	M	42	absent	moderate	"
M	47	considerable	moderate	"	F	40	slight	considerable	"
M	46	absent	considerable	"	M	36	very slight	moderate	"
M	36	slight	moderate	"	F	35	slight	slight	"
M	69	severe	severe	<i>great</i>	F	54	considerable	considerable	<i>moderate</i>
F	66	severe	severe	"	M	53	absent	considerable	"
M	66	considerable	severe	"	F	49	slight	moderate	"
M	63	severe	considerable	"	M	47	absent	considerable	"
M	63	severe	considerable	"	M	42	very slight	slight	"
M	60	severe	considerable	"	F	37	one fleck	slight	"
M	60	slight	severe	"	F	69	severe	severe	<i>slight</i>
M	59	severe	severe	"	F	65	severe	severe	"
M	57	moderate	considerable	"	M	63	severe	severe	"
M	56	severe	severe	"	F	62	slight	moderate	"
M	56	one fleck	considerable	"	M	55	severe	considerable	"
M	54	one fleck	considerable	"	M	51	severe	considerable	"
M	51	severe	severe	"	F	50	considerable	considerable	"
M	50	severe	considerable	"	F	47	absent	slight	"
M	49	slight	considerable	"	M	46	absent	slight	"
M	46	one fleck	moderate	"	M	46	moderate	slight	"
M	44	considerable	considerable	"	M	43	moderate	slight	"
M	43	severe	severe	"	M	42	absent	slight	"
F	43	very slight	moderate	"	M	40	very slight	moderate	"
M	40	absent	moderate	"	F	34	very slight	moderate	"
M	76	severe	severe	<i>considerable</i>	M	47	moderate	slight	<i>collateral cerebral circulation</i> ⁵
F	72	severe	severe	"	M	60	slight	moderate	<i>absent</i>
M	65	severe	severe	"	M	30	absent	very slight	"
M	64	considerable	considerable	"	M	24	absent	slight	"
M	63	moderate	considerable	"	F	16	absent	very slight	"
M	61	considerable	considerable	"	M	52	severe	} examination confined to head	
M	57	severe	moderate	"	M	50	absent		
M	53	—	severe	"	M	48	severe		

⁵ In this case there was no general cardiovascular hypertrophy, but the haemorrhage came from a central branch of the left posterior cerebral artery, which was hypertrophied and widened to form a collateral circulation. The left intracranial carotid, at its junction with the left middle and anterior cerebrals, was very small, its lumen being extremely narrow; the abnormality appeared on microscopic examination to be the result of an old endarteritis. The circulation was ensured by enlargement and widening of the right intracerebral carotid, the proximal portion of the right anterior cerebral, the anterior communicating artery, and particularly, the left posterior cerebral and posterior communicating arteries.

IV. *Degeneration, Intimal.*

Small dissecting aneurysms occur in the muscular arteries in cases of exceptionally severe atheroma.

V. *Degeneration, Medial.*

Rupture of arterioles may follow acute degeneration of the media, which is caused by bacterial and other poisons, or by anaemia. Among the instances of this, in 1907 to 1913, were two cases of cerebral haemorrhage due to toxæmia of pregnancy, in which there were no convulsions. The haemorrhages which result are usually small.

Of greater importance are the haemorrhages which are due to chronic medial degeneration. As is shown in Tables VIII and X, which give an analysis of such haemorrhages during 1907 to 1913, the central branches of the *cerebral arteries* are far more frequently affected than any other muscular arteries. Persistently high blood-pressure is a most important factor in their rupture. In almost all cases of such cerebral haemorrhage (*vide* Table IX) excessive blood-pressure during life is proven at necropsy by easily recognizable cardiovascular hypertrophy.

In Table VIII is given an analysis of the sites of haemorrhage in the brain in the 72 cases which occurred in 1907 to 1913. In Table IX the condition of the cardiovascular system in these cases is recorded.

TABLE X.

Direct Rupture of Muscular Arteries, other than Cerebrals; Medial Degeneration, 1907 to 1913.

Sex.	Age.	Coronary, posterior descending branch.	Hepatic in liver.	Splenic in spleen.	Renal in kidney.	Mesenteric in submucosa.	Left suprarenal in gland.	General vascular degeneration.	Cardio-vascular hypertrophy.
M	70	1	—	—	—	—	—	—	—
M	68	—	—	—	—	—	1	severe	great
M	25	—	multiple	multiple	multiple	multiple	—	severe	considerable very great

Direct rupture of *other muscular arteries* is very rare. It appears to occur only when severe degeneration is associated with marked heightening of the blood-pressure.

The cases of direct rupture, due to medial degeneration, of muscular arteries other than the cerebral, during the years 1907 to 1913 are set out in Table X, together with notes on the associated condition of the cardiovascular system.

Summary of Part VI.

Comparison of the influence of inflammations and degenerations on the formation of *true aneurysm* shows that, in the case of the large elastic arteries, syphilitic inflammation is much the most important factor, if slight diffuse

dilatation due to medial degeneration be disregarded. In the case of large muscular arteries which spring from the aorta, syphilis is the commonest cause of aneurysms close to their origin. In the case of large muscular arteries at a distance from the aorta, and the small muscular and elastic arteries, aneurysms caused by syphilis are extremely rare. In these arteries the great majority of aneurysms are caused by non-granulomatous inflammation or by degeneration. Medial degeneration is the essential degeneration. In aneurysms resulting from medial degeneration excessive blood-pressure is an important factor, unless vascular degeneration is extreme. Exceptions to this are found in saccular aneurysms of cerebral arteries. In the formation of these cerebral aneurysms congenital abnormality in structure appears to be the essential factor. Aneurysms, caused either by inflammation or degeneration, are found with few exceptions in arteries which do not lie within solid tissues. Absence of support appears, therefore, to be an important factor. The part played by loss of support is very conspicuous in aneurysms within phthisical vomicae.

Though syphilitic infection is an extremely rare cause of aneurysm of the muscular arteries at a distance from the aorta, and of the small elastic arteries, it is the commonest cause of aneurysm in general.

Direct rupture, with or without the formation of dissecting and false aneurysm, is an extremely rare result of syphilitic infection. Non-granulomatous inflammation is a common cause. The commonest cause is medial degeneration associated with abnormally high blood-pressure; the arteries which rupture under these circumstances are, with very few exceptions, the central branches of the cerebrals. In a few cases imperfect compensatory growth of the intima in elastic arteries appears to determine direct rupture (*vide* p. 241, VI).

In conclusion I should like to thank Dr. Paul Fildes and Dr. P. N. Panton for supplying the results of Wassermann tests, Dr. W. W. Woods for great assistance in the analysis of records, Dr. Fearnside for reading through the manuscript, and the members of the medical and surgical staff for allowing me free access to their notes. To Dr. G. B. Bartlett, Assistant Director of the Pathological Institute of the London Hospital, I am deeply indebted for generous help in the investigation of arteries during more than seven years.

REFERENCES.

1. Thoma, R., *Virchow's Archiv f. path. Anat. u. Physiol.*, Berlin, 1883, xciii. 443.
2. Jores, L., *Wesen und Entwicklung der Arteriosklerose*, Wiesbaden, 1903, 65.
3. Allbutt, Clifford, *Trans. Hunterian Soc.*, Lond., 1895-6, 38.
4. Johnson, George, *Diseases of the Kidney*, Lond., 1852.
5. Liddell and Scott, *Greek-English Lexicon*, Oxford, 1890.
6. Saltykow, S., *Ziegler's Beiträge z. path. Anat. u. allg. Path.*, Jena, 1908, xliii. 147.
7. Gaskell, J. F., *Journ. of Path. and Bacteriol.*, Camb., 1911-12, xvi. 287.
8. Mönckeberg, J. G., *Virchow's Archiv f. path. Anat. u. Physiol.*, Berlin, 1903, clxxi. 141.
9. Klotz, Oskar, *Brit. Med. Journ.*, 1906, ii. 1767.

10. Turnbull, Hubert M., *Trans. Med. Soc.*, Lond., 1911, xxxiv. 242.
11. Wiesner, Richard, *Frankf. Zeitsch. für Path.*, Wiesb., 1910, iv. 161.
12. Fildes, Paul, and McIntosh, James, *Brain*, 1913-14, xxxvi. 193.
13. Aitchison, C. U., *Arch. Path. Inst. of the Lond. Hosp.*, 1908, ii. 29.
14. Reuter, Karl, *Zeitsch. für Hygiene u. Infektionsk.*, 1906, liv. 49.
15. Schmorl, G., *Münch. med. Woch.*, 1907, liv. 188.
16. Wright, James Homer, and Richardson, Oscar, *Publ. Mass. Gen. Hosp.*, Boston, 1909, ii. 395.
17. McIntosh, James, and Turnbull, Hubert M., *Lancet*, Lond., 1913, i. 512.
18. Andrewes, F. W., *Report of the Medical Officer, Local Gov. Board*, 1911-12, xli. Appendix B, 209.
19. Benda, C., *Berl. klin. Woch.*, 1906, xliii. 989.
20. Strasmann, *Deutsche Zeitsch. für Nervenhe.*, Leipz., 1910, xl. 387.
21. Strasburger, Julius, *Münch. med. Woch.*, 1907, liv. 714.
22. Marchand, *vide* Aschoff, L., *Beihefte zur medicin. Klinik*, 1908, iv. 1.
23. Ponfick, *Virchow's Arch. f. path. Anat. u. Physiol.*, Berlin, 1873, lviii. 528.
24. Kamen, Ludwig, *Ziegler's Beit. z. path. Anat. u. allg. Path.*, Jena, 1895, xvii. 416.
25. Casper, M., Lubarsch und Ostertag, *Ergebn. d. allg. Path. und path. Anat.*, Wiesbaden, 1896, Abteil. iii. 50.

MUMPS: A CRITICAL REVIEW¹

By ANTHONY FEILING

THOUGH mumps may be regarded as one of the commonest infectious diseases, its usual benign course has tended perhaps to divert the attention of medical observers from what is in reality a disease of great interest. With the great increase in bacteriological knowledge of the last ten years attention has, not unnaturally, been focused on more serious and disabling infections, and it is only quite lately that any advance at all has been made towards the discovery of the infective agent in mumps. Simultaneously the numerous complications which may occur, and particularly those involving the central nervous system, have been the subject of much study. A review of the more recent literature would certainly open the eyes of many whose conception of mumps had previously been somewhat restricted. It has been the aim of the writer of this paper to bring together most of the recent literature on mumps, with special regard to the pathology—formerly an entirely unknown quantity—and to the various complications which may occur. Recently the writer undertook an investigation into the alterations in the blood in mumps, and was led to extend his observations towards the clinical aspects of the disease, both by personal observation and by an investigation of the literature. At the end of the paper will be found a table giving the results of the writer's blood examinations.

Definition.

Mumps, or epidemic parotitis, is a specific infectious disease which commonly occurs in epidemic form. It attacks for the most part children between the ages of 5 and 15, though no age can be said to be altogether exempt from infection. Whilst generally characterized by acute inflammation of the parotid gland on one or both sides, the disease may occur without it, so that the old time-honoured name of Mumps has a better claim to general use than that of epidemic parotitis.

¹ The bulk of this paper was comprised in a Thesis for the degree of M.D. Cantab. in July, 1913. Since then new material has been added and the whole largely rewritten. For permission to republish the figures of the blood examinations and other matter the writer is indebted to the courtesy of the editors of the *Lancet*.

Historical.

The disease has been known since the time of Hippocrates, who described it in his book of 'Epidemics', and observed that it was not associated with suppuration and that orchitis sometimes followed. During the last twenty years references to it have been abundant in medical literature, especially in France, where the occurrence of large epidemics amongst soldiers has afforded much material for study.

Distribution.

The disease is almost universally found; it is of course very common in Europe and America; in Australia and India large epidemics have been reported; to my own knowledge a considerable epidemic occurred recently in the Sudan.

Sex and Age Incidence.

By common consent children are far more often attacked. Uncommon below two years, its incidence reaches its maximum between the years of 5 and 15; persons above puberty appear less liable to the infection. No age, however, can be said to be absolutely exempt. Between the years 1891-1910, 1,763 persons were certified to have died of mumps in England and Wales; of these 305 were under one, 775 were under 5, and 988 between 5 and 85. These figures, however, being those of *fatal* cases, give an altogether erroneous idea of the incidence.

The sexes are equally affected. A reference to the fatal cases recorded in the period 1891-1910 shows 887 males and 876 females.

Mumps is not a disease which occurs naturally amongst the lower animals. Poore, however, reported a case where a dog developed parotitis and orchitis fourteen days after his master, a boy of 17, had suffered from the disease.

Though occurring at all times of the year, the *seasonal incidence* for most epidemics is undoubtedly the spring and autumn, and it is rare for an epidemic to occur in a school in the summer term.

Mortality.

The total annual mortality for mumps in England and Wales for the years 1891-1910 varied from a minimum of 54 to a maximum of 118, the death-rate being fairly constant at 3 per million. This rate of course gives no indication whatever as to the total number of cases; all we can say definitely is that the case mortality is extremely low. The disease appears to be most fatal in children under five, especially in infants under one year.

Incubation—Quarantine.

According to the Report of the Clinical Society in 1892 the incubation period is usually 21 days, the extreme limits being from 12 to 25 days. Bloomfield has reported an incubation of 26 days, Penny of 27 days, and Douglas one of 29 days. Dukes, from observation of 23 cases infected by one boy, states that the incubation varied from 16 to 23 days, the largest number being 17 days. Manine, from an investigation of two large epidemics in French cruisers, found the longest incubation period to be 19 days and the shortest 5 days. So short a period as the latter, however, is exceptionally rare. In only 4 of the writer's cases was he able to fix the incubation accurately; it was as follows:

In 2 cases 22 days.

„ 1 case 17 „

„ 1 „ 19 „

It appears fairly established that there is a prodromal stage before the appearance of the characteristic parotitis, during which infection is possible; this stage the Clinical Society recommended should be assumed as four days. The duration of the contagion probably progressively diminishes from the onset of the parotitis and ceases three weeks after its first appearance. Sharp, however, relates the cases of two patients who remained sources of infection for six weeks.

From what has been said it may be inferred that the period of quarantine should, strictly speaking, be not less than twenty-five days, but since it is fairly certain that mumps is not infectious till, at most, four days before the appearance of the parotitis, the first week or ten days of this quarantine may safely be omitted.

Infection is probably always by direct contagion from person to person.

Immunity.

One attack usually confers lifelong immunity; the writer has found great difficulty in proving authentic cases of a second infection.

Pathology.

Since the mortality from mumps is strikingly low it is not surprising to find that practically nothing is known of its morbid anatomy; and the exact nature of the changes which occur in the salivary glands, testicles, or other organs is still a matter of some doubt. Virchow described the condition of the parotid gland as one of inflammatory serous and cellular infiltration of the intra-acinous and periacinous tubules. Sicard and Dopter have endeavoured to throw light on the morbid process by examining the saliva from Stenson's duct. They find that, whereas the normal saliva is free from all formed elements, in mumps numerous cells appear: at first lymphocytes, large mono-

nuclear and polynuclear leucocytes: later a regular glandular desquamation seems to take place with the liberation of casts. As the swelling of the glands subsides the cellular elements disappear from the saliva. From Gordon's experiments, to which reference is made later, it would appear that the swollen glands are the seat of an acute interstitial inflammation. Various attempts have been made by bacteriological and experimental methods to elucidate the nature of the infection. In 1893 Laveran and Catrin published the first observations of this kind. By aspiration of the inflamed parotid glands they obtained a diplococcus in sixty-seven out of ninety-two cases; in twelve out of sixteen cases of orchitis a pure culture of the same organism was found. Their inoculation experiments with animals, however, were unconvincing, as they failed to reproduce anything resembling mumps as seen in the human subject. Mecray and Walch in 1896 and Michaelis and Bienn in 1897 also obtained a diplococcus in pure culture from Stenson's duct. Busquet and Feri in 1896 cultivated a diplococcus from the blood in all of twenty cases examined. Fichera, on the other hand, in 1904 obtained absolutely negative results. He examined bacteriologically the blood, the liquid from the tunica vaginalis testis, and the fluid from the testicle itself in six cases of mumps complicated by orchitis. Cultures remained sterile, and he believed the diplococcus obtained by previous observers to be the *Staphylococcus epidermidis albus*.

Teissier and Esmein in 1906 again discovered a diplococcus by cultivation of the blood and saliva from Stenson's duct; blood cultures were positive in thirty-seven out of forty-five cases, cultures from the saliva in two out of ten only. They stated that the organism was Gram-positive; that found by Laveran and Catrin was described as Gram-negative. The animals inoculated by Teissier and Esmein invariably succumbed to a fatal septicaemia, so that their experiments again fail to convince.

Herb in 1909 conducted experiments on similar lines. She obtained a diplococcus post mortem from the lungs, testicles, cerebro-spinal fluid, bile, and parotid glands of a man who died shortly after a disease which resembled mumps; the fact, however, that a *suppurative* parotitis was found at the autopsy at once throws doubt on the original diagnosis of mumps. Cultures of this diplococcus produced an acute interstitial inflammation, without suppuration, when injected into the testes of rabbits and the parotid glands of dogs and monkeys.

None of the experimental observations thus briefly reviewed can be said satisfactorily to have isolated the causal organism of mumps. The most recent work on the subject, however, has a better claim to this distinction. Almost simultaneous experiments were made by Nicolle and Conseille in France and by Gordon in this country, working quite independently.

Nicolle and Conseille were quite unable to find any micro-organisms in the fluid obtained by aspiration of the parotid glands of patients with mumps. They then proceeded to inject the fluid thus obtained into the parotid glands of monkeys. All three experimental monkeys developed, after an incubation

period varying from sixteen to twenty-six days, a febrile illness lasting two to seven days: one monkey suffered from a definite swelling of the left parotid gland with evident pain on movement of the jaws. They further examined the blood of one of their monkeys and found a mononuclear leucocytosis, strictly comparable to that exhibited by the child from whose parotid gland the fluid for inoculation had been originally obtained. The first monkey had recovered from its febrile attack when the third was inoculated: it was therefore inoculated with the same material as the third monkey and this time failed to develop any febrile illness, the inference being that immunity had been conferred by the first inoculation.

Gordon's experiments were briefly as follows: Patients in whom the clinical diagnosis of mumps was obvious were asked to gargle about 100 c.c. of sterile saline solution; in some cases the parotids were massaged at the same time. The mixture of saliva and saline thus obtained was passed through a Berkefeld filter. This filtrate was used for all his inoculation experiments. In every case a broth culture of the filtrate remained sterile. The filtrate was then injected into the brains of several monkeys; some were also injected into the peritoneal cavity. Out of ten monkeys thus injected five appeared to be unaffected, four died, and one became ill but recovered later. An experiment was made with the filtrate previously heated to 55° C.; the animal was unaffected, while another injected with the same material, but unheated, died on the fifth day. All the monkeys that died exhibited symptoms suggesting meningeal irritation. In one of them a lumbar puncture was made during life; the cerebro-spinal fluid was slightly turbid and contained 1,500 cells per c.c., of which 82 per cent. were lymphocytes; cultures of the fluid remained sterile.

The brains, spinal cords, and parotid glands of four of these monkeys were submitted to careful histological examination. In every case distinct changes were found in the nervous system, consisting of infiltration of the pia arachnoid with lymphocytes and degenerative changes in the nerve cells of the cortex cerebri and anterior horn cells of the spinal cord. In three of the cases the parotid glands appeared healthy, in the fourth case an acute interstitial parotitis was present with distinct foci of lymphocytic infiltration; this monkey survived the injection longer than the other three.

These experimental findings are of great interest in view of the numerous cases of severe nervous complications which are well known to occur occasionally in man in the course of mumps. From his experiments, which are admittedly of a preliminary nature, Gordon concludes that mumps is apparently due to a filterable virus comparable to that of poliomyelitis, small-pox, and typhus; that the virus can pass through a Berkefeld filter and is destroyed at 55° C.

Here the question of the pathology of mumps must be left. Other observers may perhaps confirm Gordon's results, which are already full of promise for an ultimate solution of the problem.

Changes in the Blood.

Few observations appear to have been made on the blood in mumps, and the subject is not even mentioned in most text-books. Gulland and Goodall state 'that the blood shows no change in uncomplicated cases', and 'orchitis seems generally to produce a slight leucocytosis'. In 1902 Sacquépée published a paper entitled 'Formule hémoleucocytaire des oreillons' based on the results of the examination of twenty cases. He concluded that cases without orchitis exhibited a slight leucocytosis, varying from 6,000 to 13,600 per cubic millimetre, with a relative increase of the mononuclear elements, while the appearance of orchitis was accompanied by an increase in the number of polymorphonuclear leucocytes. Wile in 1906 examined twenty cases; he quotes first the observations of Krestnikow and Pick. Krestnikow found a lymphocytosis present from the onset of the disease and further noticed an increase in the polymorphonuclears when orchitis occurred. Pick considered that the absence of a polymorphonuclear leucocytosis was of value in differentiating the orchitis of mumps from the gonorrhoeal form. Wile's most important conclusions from his own results were that (i) lymphocytosis is a constant feature; (ii) it is present on the first day of the disease and persists until all swelling has disappeared; (iii) it is most marked in children; (iv) with the advent of orchitis there is an increase in the polymorphonuclear count; (v) there is no secondary anaemia.

Barach examined the blood in eleven cases and found a leucopenia, most marked in the more severe cases, a relative decrease in polymorphonuclears, and a relative increase in lymphocytes.

The writer has examined the blood in forty-two cases. At the end of this paper a complete table of the results is given. His conclusions were as follows:

- (i) That the blood in mumps shows definite changes in the corpuscular content.
- (ii) That these changes consist
 - (a) in a slight increase in the total number of leucocytes;
 - (b) in a lymphocytosis, which is both relative and absolute.
- (iii) That this lymphocytosis is present on the first day of the disease and persists for at least fourteen days.
- (iv) That the occurrence of orchitis does not invariably alter the blood picture.
- (v) That the changes in the blood are of distinct diagnostic value in differentiating mumps from other inflammatory swellings of the parotid or submaxillary salivary gland.

Symptomatology.

The disease is so familiar that it is hardly necessary to do more than refer very briefly to the characteristic symptoms. These consist of the sudden appearance of some pain or stiffness at the angle of the jaw, with slight constitutional symptoms, headache, and fever varying from 99° to 101° F. Soon, perhaps the next day, an obvious swelling of one or both parotid glands is noticed; usually one gland is affected first, to be followed by the other in two to three days' time. The swelling is rather diffuse and soft, situated in the position of the parotid gland and filling up the hollow between the ear and the angle of the jaw. The skin is generally not red, nor is there any marked tenderness on palpation, save in cases of extreme swelling; fluctuation is never observed. Slight enlargement of the neighbouring lymphatic glands may occur. It is the exception rather than the rule for the submaxillary glands to be involved. Catrin, however, gives the incidence of submaxillary inflammation as 50 per cent. The swelling persists for about seven to ten days; by the twelfth day all swelling has usually disappeared. Fever is usually present for the first two to three days: even in uncomplicated cases a temperature of 101° to 103° F. is not uncommon; the fever is wont to fall when the parotid swelling reaches its height. One almost constant sign is the unusual appearance of the orifice of Stenson's duct, which stands out as a bright red papilla. In the vast majority of cases complete recovery has occurred within three weeks, with no permanent ill effects.

But in a certain number of cases—and these more commonly adult persons—mumps is by no means the benign disease with which every one is familiar. Many complications of great interest to the physician, as well as serious to the patient, occur. These may be grouped as follows:

- (i) Abnormal modes of onset;
- (ii) Orchitis;
- (iii) Pancreatitis;
- (iv) Nervous complications;
- (v) Affections of the special sense organs;
- (vi) Nephritis;
- (vii) Certain rare complications.

Abnormal Modes of Onset.

Very severe prodromal symptoms are sometimes observed. Catrin noticed rigors, severe headaches, night sweats, and, very commonly, inflammation of the posterior pharyngeal wall. Orchitis may be the first symptom. Thus Torpey mentions a case where the left testicle became inflamed on December 3 and the right testicle on December 7; on December 17 double parotitis appeared. Waddelow reports acute epididymitis in a man of eighteen followed the next day by parotitis. The writer has seen an interesting case where a swelling appeared

in the left epididymis on February 12, with a fever of 102° F.; on February 14 double parotitis appeared; on February 18 both submaxillary glands were swollen: the body of the testicle did not become involved till the swelling of the parotid and submaxillary glands was subsiding.

Meningeal symptoms of some gravity may usher in the disease. Colomb and Mercier report the case of a French soldier who was one day found comatose on the floor of his room; the pupils were dilated, the neck stiff, Kernig's sign was marked; the coma lasted three days, when the pulse and temperature, which had both been raised, suddenly fell and a double parotitis manifested itself. Apert has seen an eruption of herpes zoster forty-eight hours before the appearance of the parotid swelling.

Orchitis.

Of all complications orchitis, or metastasis to the testicle, as it was formerly called, is undoubtedly the commonest. Its frequency has been variously estimated; the proportion of cases attacked bears a constant ratio to the ages of the patients: boys under puberty may be said to be practically exempt. Catrin states that when males of all ages are included orchitis occurs in 16 per cent. Dukes, in an epidemic of twenty-three cases, all infected by one boy, found orchitis in 37.5 per cent., and in another epidemic of thirty cases 20 per cent. Chauvin reported nineteen cases out of sixty-five, a percentage of 29. The date of its appearance varies considerably. As already mentioned, it may be the first manifestation, more often it occurs during the height of the disease. Chauvin found its appearance to vary from the third to the eighteenth day of the disease, Dukes from the third to the eighth, being observed in the majority of the cases on the seventh day. It is an old observation that orchitis seldom occurs in patients who are kept in bed a full week. Dukes, however, in one epidemic, found, contrary to his previous experience, that out of thirty cases 20 per cent. developed orchitis, though all had been confined to bed for eight days.

Regarding the actual seat of the lesion, it is generally assumed, and stated in most text-books, that the body of the testicle is the part involved first, and that it is therefore a true orchitis. The writer, however, holds the view that in the first instance the epididymis is affected, the body of the testicle being involved later. Opinions on this point have varied. Trousseau in one case noted that 'one of the testicles and particularly the epididymis were swollen'. Laveran, Guinon, and Comby all state that while the epididymis is occasionally involved the brunt of the disease falls on the body of the testicle. Catrin and Dieulafoy, however, maintain that the epididymis is first attacked. Chauvin paid particular attention to this point, and in a series of nineteen cases found that the epididymis and body were affected in fifteen cases, the epididymis alone in two cases, the body alone in three cases, and the vasa deferentia alone in three cases. In the signs and symptoms of the orchitis itself there is nothing peculiar. Pain, swelling, and tenderness, often with high fever, were present. Fortunately one

testicle only is usually attacked. In adults severe nervous symptoms not infrequently accompany the orchitis. Thus Philips has reported the case of a man of twenty-three in whom each epididymis became separately inflamed, and with the appearance of each epididymitis high fever, rigors, delirium, and stupor occurred. Mitchell describes acute delirium occurring in a patient whose undescended testicle became the seat of an orchitis during mumps. The serious part of the orchitis is, of course, the subsequent atrophy of the testicle which not very infrequently follows. Statistics as to the exact proportion of cases followed by atrophy are lacking, but the number is certainly considerable. Occasionally, as in a case of Lebouillet, the atrophy succeeds very rapidly, in three weeks even. In a case observed by the writer complete atrophy seemed to have occurred in six weeks.

Pancreatitis.

More or less severe abdominal symptoms occasionally occur during an attack of mumps. They consist of pain, generally sudden in onset, and of incessant and sometimes uncontrollable vomiting: haematemesis has been reported. On palpation there may be marked tenderness in the epigastrium and occasionally an elongated tumour has been felt stretching transversely across the abdomen. Such symptoms are ascribed to pancreatitis, an hypothesis which receives some support from the facts that undigested fat has been found in the stools, from the post-mortem examination of at least one case, and from a careful study of clinical symptoms. Cheinisse, in a critical review, gives an excellent summary of the subject. Though suggested by earlier writers, the occurrence of pancreatitis was first described by Cuche in 1897. Simonin, in discussing the symptomatology, places pain in the first place; this is spontaneous and situated in the epigastrium; nausea and vomiting are the next most constant features; in five cases out of ten diarrhoea was present, in two constipation. Freund reported eight cases with similar symptoms, in one of which a tumour could be felt in the epigastrium. Raymond in an epidemic of sixty cases diagnosed pancreatitis in four. Sharp in an extensive epidemic observed that nine cases suffered from severe abdominal symptoms, specially pain and vomiting; haematemesis occurred once and in three cases blood and undigested fat were found in the stools; in every case the onset of the symptoms was abrupt and their duration limited. Edgecombe found that out of thirty-three cases of mumps in a boys' school five presented symptoms of pancreatitis; in every case the following symptoms occurred: vomiting, epigastric pain and tenderness, constipation, some fever, acetone and diacetic acid in the urine, sugar being absent. In one case a tender swelling could be felt lying transversely across the epigastrium and left hypochondrium. The urine of one case, collected on the second day of the abdominal symptoms, was examined by Cammidge, who gave the following report: 'A well-marked pancreatic reaction, indicating active inflammation of the pancreas; well-marked deposit of oxalate crystals such as is frequently

found in pancreatitis, large amounts of acetone and diacetic acid in the specimen, indicating abnormal tissue waste, and such as are generally found in those cases of pancreatic disease in which the lesion has resulted in severe glycosuria.'

Jacob reports a case of acute abdominal pain and vomiting in mumps, in which a definite sausage-shaped mass was felt in the epigastrium; in a week it had completely disappeared. Harris describes a case of diabetes mellitus following mumps; one month after recovery from mumps polyuria had been observed and three years later a typical case of diabetes had declared itself. Glycosuria has been very seldom observed during attacks of mumps; Barbieri, however, has described the case of a child of six who, on the seventh day of the disease, suffered from acute abdominal pain, vomiting, and diarrhoea; polyuria and glycosuria were present and lasted fifteen days; a large amount of fat was also found in the faeces.

The writer has been able to find the record of only one autopsy on a case of pancreatitis in mumps. Lemoine and Lepasset published the case in 1905 with a full account of the post-mortem findings. The patient exhibited the usual signs and symptoms of mumps, with orchitis, till the fourteenth day of the disease, when vomiting began, to be quickly followed by jaundice; the clinical picture of an icterus gravis rapidly appeared, and in four days the patient died after a profuse haematemesis. At the autopsy it appeared that the jaundice was caused by an enlarged gland pressing on the common bile duct. The pancreas was congested, swollen, and oedematous; microscopically the epithelial cells were swollen and degenerated, compressing the islets of Langerhans. The liver was also very much congested.

Reviewing the evidence available we are forced to the conclusion that the existence of pancreatitis as an occasional complication of mumps is fairly proved. In children it is probably the commonest cause of pancreatitis.

Nervous Complications.

Symptoms of serious disturbance of the functions of the central nervous system are not very uncommon in mumps; they are probably always due to some actual organic lesion of an inflammatory nature, though exact proof is generally lacking. Any part of the central nervous system may be attacked, but it will be convenient to classify them.

(a) *Cerebral and meningeal lesions.* Severe transitory disturbances of the cerebral functions are common both at the onset and during the course of the disease. Headache, delirium, convulsions, and high fever amounting sometimes to hyperpyrexia may all occur. In a case of the writer's delirium persisted for three days. Gallavardin considered that such symptoms were most common in adult males and preceded the appearance of orchitis. In some cases death has rapidly succeeded; Hamilton reported the case of a young man who

died with acute mania on the second day of the disease. Maximowitsch, in an autopsy on a case dying with convulsions, found the surface of the brain oedematous, the sulci filled up with semi-fibrinous exudation—a condition termed by Gallavardin serous meningitis.

Tremors and involuntary movements have been observed, sometimes choreiform in type. Lafforgue has described a case of paramyoclonus, which recovered after six weeks' duration. But symptoms of a more serious and persistent nature have occurred, such as hemiplegia and aphasia.

Monro in 1883 reported the case of a man who, after recovery from an attack of mumps complicated by orchitis, delirium, and hyperpyrexia, suffered from unsteadiness of gait, incoordination of speech, and agraphia. Sorel observed aphasia in a patient in whom delirium and orchitis occurred; the aphasia persisted for fifteen months when recovery gradually ensued.

Lannois and Lemoine again have described a case of right hemiplegia and aphasia recurring a week after the appearance of the parotitis; gradual recovery took place. These authors, in discussing the possible nature of the lesion, mention the theories of Eichorst, who suggested a passive cerebral congestion dependent upon compression of the jugular vein by the parotid gland, and of Jaccoud and Appleyard, who suggested embolism from an acute endocarditis. They conclude that a diffuse meningo-encephalitis is in all probability the lesion present. Findlay in 1906 reported a case of infantile hemiplegia following mumps after a few days' interval. Thus it is seen that clinical observations alone raise a strong presumption in favour of the possibility of the virus of mumps attacking the nervous structures of the brain itself; when we come to the investigation of meningitis we are on surer ground, thanks to the modern diagnostic use of lumbar puncture and cytological examination of the cerebro-spinal fluid.

Monod was the first to demonstrate the occurrence of lymphocytosis of the cerebro-spinal fluid in mumps, even in cases where there was no clinical evidence of meningitis. Since then many cases have been investigated and the lymphocytosis has been a constant feature. Chauffard and Boidin have described two cases whose interest lies in the repeated examinations of the cerebro-spinal fluid; in both a marked lymphocytosis was present, which in one case persisted till the forty-sixth day of the disease. The only clinical symptoms of meningitis were headache, insomnia, and a slow pulse-rate (60-70). These authors, however, state that the increase of the cells of the fluid was so great as to constitute '*une véritable suppuration lymphocytaire*'. Nobécourt and Brélet recorded a similar case. Acker has described two cases of parotitis complicated by meningitis; in the first case the cerebro-spinal fluid was normal; in the second a marked lymphocytosis was present. The latter case died; at the autopsy there was found great congestion of the veins on the cortex of the brain, much increase of serous fluid in the ventricles, and a definite meningitis at the base of the brain with plaques of fibrin; the brain substance itself was normal. Post-mortem evidence is also forthcoming in

a case reported by Bien. A child of eight died on the eighth day of the disease with severe convulsions. The cerebral meninges showed hyperaemia and a slight opacity, and microscopically inflammatory infiltration: there was also found an absence of myelin in the medullary layers of the cortex. Bien considered that a definite leptomeningitis and encephalitis was present. The writer has personally observed one case of meningitis following mumps. The patient was a male child aged $5\frac{1}{2}$, who on the fourth day of an attack of mumps complained of headache; two days later he became practically comatose, with absence of knee-jerks. Lumbar puncture revealed a slightly turbid fluid containing albumin, 0.125 per cent., and 2,500 cells per c.c., of which 96 per cent. were lymphocytes: the fluid was sterile. Complete recovery ensued. Lister and Fearnley record a case where the operation of trephining was performed for the relief of the meningitis of mumps; 'choked disks' were found and the respiration began to fail; the skull was trephined four inches above the mastoid; much clear cerebro-spinal fluid escaped and a perfect recovery was finally made.

Roux has summarized most of the published cases and from these and his own cases concludes:

(i) That while meningeal symptoms are frequent, typical meningitis is rare.

(ii) That it generally occurs at the height of the disease, but on rare occasions may even precede the parotid swelling.

(iii) There is almost always a very marked lymphocytosis of the cerebro-spinal fluid.

(iv) The symptoms usually subside rapidly.

(b) *Lesions of the cranial and peripheral nerves.* Associated with meningeal symptoms various cranial nerve affections are reported. Dopter describes a case where, on the fifteenth day of the disease, double orchitis appeared, and at the same time left facial paralysis, paresis of the right half of the palate, and dilatation of the left pupil with paralysis of accommodation. A marked lymphocytosis of the cerebro-spinal fluid was found. Four years later he reported a case of herpes in the distribution of the third division of the fifth nerve, with loss of sensation in the whole area of distribution of the nerve, again accompanied by a lymphocytosis of the cerebro-spinal fluid and with clinical symptoms suggestive of meningitis, severe headache, and vomiting. Sicard observed a similar case with an herpetic eruption in the distribution of the supra-orbital and auriculo-temporal nerves nine days after the appearance of a double parotitis; headache, vomiting, stiffness of the neck, and lymphocytosis of the spinal fluid were all present.

Facial paralysis has been observed by Dopter, Daireaux, Courand and Petges, Lacroix, and Hirtz. In an epidemic of sixty cases of mumps Courand and Petges saw seven cases of facial paralysis: it appeared at a time varying from three to nine days after the onset of the disease; it was always unilateral, lasted from six to ten days, and disappeared completely without treatment.

They considered that it was due to direct compression of the nerve by the swollen parotid gland. Other suggested causes are a basal meningitis and a toxic neuritis. That the latter theory is more likely to be correct would appear from the following considerations: (i) that facial paralysis is very rare in cases of swelling of the parotid glands from other causes; (ii) that in some cases a loss of taste has been demonstrated; (iii) that in one case (Hirtz) the reaction of degeneration was present in the muscles supplied by the facial nerve.

Cases suggesting a peripheral neuritis or a toxic polyneuritis are reported. Thus in a case of Joffroy a complete flaccid paralysis of all four limbs appeared on the twentieth day of the disease; the deep reflexes were lost, and there was diminution of cutaneous sensibility; complete recovery followed. Chavanis and Révilliod report two similar cases. Gallavardin observed the case of a man aged 31 who, on the eighth day of the disease, experienced subjective sensory disturbances in the arms and legs; seven days later complete flaccid paralysis of all four limbs occurred; the deep reflexes were abolished, there was muscular atrophy and diminution of response to the faradic current; recovery was slow but eventually perfect. These cases are strictly comparable to the cases of polyneuritis which occasionally occur in other infectious diseases, such as influenza; from the clinical signs and symptoms we are justified in assuming the existence of a toxic neuritis. The prognosis is invariably good.

(c) *The spinal cord.* Evidence of involvement of the spinal cord in mumps is scanty. Missimilly, however, has recorded a case of what he termed 'poliomyelitis' in mumps. The patient was a child aged 5, who, a few days after the onset of mumps, developed a complete flaccid paraplegia: several months later the paralysis had disappeared, except in the left thigh, where there was much muscular atrophy, with the reaction of degeneration in the wasted muscles.

Warrington has described a case of great interest where an ascending myelitis occurred ten days after the appearance of what was diagnosed as mumps: there was complete flaccid paraplegia with absence of reflexes; incontinence of urine and a patulous anus, with anaesthesia to a segmental level, completed the picture. Finally, as the disease spread up the cord, death occurred from paralysis of the diaphragm.

Sicard has described an unusual case of hydrocephalus, which he regarded as having followed the meningitis of mumps. The patient was aged 15 and presented, besides an obvious hydrocephalus, a spastic diplegia, associated with an intention tremor, asynergia, nystagmus, and a scanning speech. Two years before the patient had had mumps during which a characteristic meningeal syndrome had been present, with marked lymphocytosis of the cerebro-spinal fluid; some weeks later headache and vertigo appeared, the other symptoms gradually making their appearance.

Lesions of the Organs of Special Sensation.

(a) *Aural complications.* Deafness of sudden onset and often permanent has been not infrequently observed. Lannois, in a review of the subject, quotes several authorities. Thus Gallavardin in 1898 collected reports of fifty-four cases. May in 1900 collected fifty-eight from the literature and added five of his own. From these accounts it would appear that premonitory symptoms such as tinnitus and vertigo commonly occur. Deafness follows more or less suddenly, usually between the first and fourth days of the disease; it is in most cases complete and permanent. Minor has reported eight cases of ear disease in mumps; in three of these the middle ear only was affected, in three the internal ear only; in one case the lesion appeared to begin in the semicircular canals and to extend to the cochlea. Voss has recently collected most of the published cases, together with four of his own. Most authorities seem agreed that the lesion should be located in the labyrinth; Ménière considered it more likely that the lesion was a meningitis at the base of the brain, a supposition to which Voss subscribes, and further adds the suggestion that in some cases a central lesion may be responsible. The meningeal hypothesis certainly receives support from the not very uncommon implication of the seventh nerve in cases complicated by symptoms of meningitis. For the moment the exact pathology of this variety of deafness must be left unsettled. It is well to emphasize the gravity of the prognosis, permanent deafness being the usual result. Jones, in describing a case of sudden and absolute deafness occurring on the sixth day of the disease, discusses its treatment by pilocarpine injections, and quotes Yearsley as follows: 'Considering the excellent results obtained by the use of pilocarpine, no case of labyrinthine deafness due to mumps should be allowed to go uncured.' In Jones's case, however, no benefit followed this method of treatment.

(b) *Ocular complications.* Affections of the eye in mumps are fortunately very rare, but a certain number of cases have been reported in which serious complications have occurred. Optic neuritis, followed by atrophy, has been the lesion most commonly observed. Talon in 1883 reported a case of a patient who developed optic neuritis one month after an attack of mumps; atrophy of the nerve followed. Blanchard in 1899 described double neuro-retinitis followed by atrophy. Woodward in 1907 reported at length the case of a young girl aged 11, who three weeks after an attack of mumps began to suffer from vertigo, lachrymation, and suffusion of the left eye; the optic disk was oedematous, but owing to haziness of the cornea no very definite view was obtained; five months later the eye was completely blind; $3\frac{1}{2}$ years later the eyeball was enucleated for an anterior staphyloma, when the optic nerve was found to be completely atrophied and replaced by connective tissue. Antonelli collected eighteen reported cases of optic neuritis complicating mumps.

Other lesions are recorded. Thus Mandonnet has observed complete paralysis of accommodation occurring during convalescence, associated with paralysis of the soft palate: both completely disappeared in a few weeks.

Le Roux describes a case of toxic amblyopia, with a central scotoma for green and red; the symptoms appeared fifteen days after the onset of the parotitis; six weeks later vision was normal. Cases of conjunctivitis, keratitis, or iritis appear to be extremely rare, and I have not met with any recorded instance.

Nephritis.

This again is a rare event in mumps, but one which has once at least been confirmed by autopsy. Catrin, in reviewing the reported cases, quotes a case described by Colin. A man, aged 24, after an attack of mumps, developed general oedema with ascites; the urine contained 22 grammes per litre of albumin; he died in coma following an epileptiform convulsion. At the autopsy the kidneys were large; the cortex yellowish with irregular whitish spots; microscopically an interstitial and an epithelial nephritis was found. Albuminuria undoubtedly occurs not infrequently in adults affected by mumps; in children it is less common. Croner, however, reported a case of nephritis following mumps in a child of 2 years; fifteen days after the onset of the parotitis oedema with haematuria and albuminuria appeared: symptoms remained for three weeks.

Troussaint has recorded the case of a man who on the sixth day of an attack of mumps was suddenly seized with violent convulsions followed by coma; oliguria was present. The following day the urine contained a large amount of albumin and many epithelial casts: complete recovery ensued.

Miller gives a summary of thirty cases from the literature, and includes one from his own practice. A child of 4 years developed on the tenth day of the disease a marked anaemia with some puffiness of the eyelids; the next day the urine was smoky, contained 5 per cent. albumin, granular casts, and red blood cells. He considered that nephritis was more likely to occur during early convalescence, and noticed that in the cases reported males were more often affected than females. It seems to bear no relation to the incidence of orchitis. The writer has personally observed one case only of nephritis, which followed rapidly upon an attack of mumps. In this case, a girl aged $3\frac{1}{2}$, oedema of the eyelids and ankles with smoky urine and albuminuria appeared fourteen days after the first appearance of parotitis; later casts were found in the urine, so that no doubt remained that a true nephritis was present. At the present moment complete recovery seems to have taken place, and the urine is free from albumin.

Certain other more rare complications deserve notice. Thus Simonin has described an acute inflammatory swelling of the thyroid gland accompanied by tachycardia and tremors; complete recovery followed. Oedema of the chest wall is a peculiar symptom which has once come to the writer's notice; Catrin refers to its occurrence in an epidemic of 159 cases observed by him in 1893.

Hirtz and Salomon have recently reported four cases of phlebitis in mumps occurring in the same family and in the same epidemic.

Diagnosis.

In the great majority of cases this is obvious. Other inflammatory affections of the parotid glands are rare; they may occur from a septic condition of the mouth, especially following abdominal operations; in such cases the usual signs of inflammation are more marked, with redness of the skin, greater tenderness, and oedema of the surrounding tissues. Suppuration may occur, an event so exceedingly rare in mumps that it is doubtful if it has really ever taken place.

Finally an examination of the blood, and especially a differential leucocyte count, will probably give the clue to a correct diagnosis; for whereas in mumps a lymphocytosis is present, in other inflammatory conditions of the glands a polymorphonuclear leucocytosis will be found.

Epididymitis, especially when it appears before the parotitis, may cause considerable difficulty in diagnosis; in cases of doubt examination of the blood will again be of value; in any case time would almost certainly provide a definite answer.

The nervous complications may arouse justifiable fears of more serious lesions, such as tuberculous meningitis, vascular lesions of the brain, or polyneuritis due to other causes. Here again clinical pathology, in the shape of an examination of the cerebro-spinal fluid as well as of the blood, will help to provide a correct opinion; time also will furnish a clear answer, since these complications run a course almost invariably to complete recovery.

It is hardly necessary to add that exposure to infection should carry weight as a factor in the diagnosis.

Prognosis.

On the whole this is uniformly good. Seeing how common is the disease deaths are exceedingly rare. In children the prognosis is always excellent. In males above puberty the risk of orchitis with subsequent testicular atrophy must be taken into account, but provided that care be taken and adequate rest insisted upon a good prognosis is justified. As we have seen, the prognosis is still good, even when apparently serious complications in the nervous system occur.

Persistence of the parotid swelling with subsequent sclerosis of the gland is so rare as to be a negligible factor in prognosis; the writer has seen one case where the swelling persisted for nearly four weeks, after which it rapidly disappeared; Thomson, however, has reported one case where the swelling had persisted for seven years.

Treatment.

No known remedy is available which has any direct control over the course of the disease. In all cases rest in bed should be insisted upon till all the swelling of the glands has disappeared; in this way complications possibly may be averted. In adult males this injunction is specially important: to avoid orchitis rest in bed should be enjoined for at least eight days; even then a certain number of cases will probably be affected by it. The usual principles as to diet, regulation of the bowels, and a gradual return to the duties of ordinary life hold good as in other febrile diseases. The complications are dealt with symptomatically as they arise and call for no special treatment beyond that commonly prescribed.

Reference has already been made to the rules which should be obeyed in assigning a period of isolation and quarantine; three weeks may be taken as an ample period of isolation.

In all epidemics strict isolation of cases should always be provided where possible.

Blood Examination Table.

Case No.	Total white blood count.	% of Poly-morphs.	% of Lym-phocytes.	Total No. of Poly-morphs.	Total No. of Lym-phocytes.	Day of Disease.	Age.	
1	9,800	57	33	5,586	3,234	13th	8	Slight leucocytosis. Relative and absolute lymphocytosis.
2	7,800	34.5	63	2,652	4,914	6th	6	Relative and absolute lymphocytosis.
3	7,200	46	50.5	3,312	3,600	?	8	Relative and absolute lymphocytosis.
4	7,800	44	47	3,432	3,666	1st	3	Slight relative and absolute lymphocytosis.
5	9,200	55	42	5,060	3,864	2nd	7	Relative and absolute lymphocytosis. (Slight leucocytosis.)
6	14,900	54.5	40	8,195	5,960	5th	5	Leucocytosis. Relative and absolute lymphocytosis.
7	9,200	53	45	4,876	4,140	4th	4½	Slight leucocytosis. Relative and absolute lymphocytosis.
8	5,600	31	66	1,736	3,696	17th	26	Slight leucopenia. Relative and absolute lymphocytosis.
9	10,000	36	60	3,600	6,000	8th	13	Slight leucocytosis. Relative and absolute lymphocytosis.
10	8,400	45	62	3,780	5,208	6th	17	Slight leucocytosis. Relative and absolute lymphocytosis.
11	4,600	34.5	59	3,430	5,782	3rd	13	Slight leucopenia. Relative and absolute lymphocytosis.
12	8,000	63.5	31	5,040	2,480	6th	7	Slight lymphocytosis only.
13	5,200	45	47	2,340	2,444	4th	9	Relative lymphocytosis.
14	9,600	45.5	49	4,268	4,904	4th	5	Slight leucocytosis. Relative and absolute lymphocytosis.
15	11,400	25.5	67	2,907	7,598	4th	2	Slight leucocytosis. Relative and absolute lymphocytosis.
16	10,600	42	53	4,252	5,618	3rd	6	Slight leucocytosis. Relative and absolute lymphocytosis.
17	14,000	43.5	51.5	6,090	7,210	2nd	5	Leucocytosis. Relative and absolute lymphocytosis.
18	12,400	64	30	7,963	3,720	2nd	6	Slight leucocytosis, practically normal proportions. ? Mumps.
19	11,400	58	39	6,612	4,446	9th	14	Slight leucocytosis. Slight relative and absolute lymphocytosis.
20	11,400	44	52	5,016	5,928	6th	13	Slight leucocytosis. Relative and absolute lymphocytosis.
21	12,200	45	51	5,470	6,222	11th	14	Slight leucocytosis. Relative and absolute lymphocytosis.

Blood Examination Table (continued).

Case No.	Total white blood count.	% of Poly-morphs.	% of Lym-pho-cytes.	Total No. of Poly-morphs.	Total No. of Lym-pho-cytes.	Day of Disease.	Age.	
22	9,600	55	42	5,280	4,032	7th	13	Slight leucocytosis. Relative and absolute lymphocytosis.
23	8,400	58	37	4,872	3,108	3rd	14	Relative and absolute lymphocytosis (slight).
24	15,600	45	51.5	7,040	8,112	9th	14	Leucocytosis. Relative and absolute lymphocytosis.
25	11,600	49	48	5,684	5,568	6th	38	Slight leucocytosis. Relative and absolute lymphocytosis.
26	13,000	41	52	5,330	6,760	3rd	6	Leucocytosis. Relative and absolute lymphocytosis.
27	9,200	41	54	3,772	4,968	5th	6	Slight leucocytosis. Relative and absolute lymphocytosis.
28	12,400	28	68.5	3,472	8,432	3rd	6	Slight leucocytosis. <i>Marked</i> lymphocytosis (relative and absolute).
29	10,000	62	36	6,200	3,600	5th	5	Slight leucocytosis. Slight relative and absolute lymphocytosis.
30	11,800	51	40.5	6,018	4,779	2nd	8	Slight leucocytosis. Relative and absolute lymphocytosis.
31	8,800	43	54	3,784	4,752	5th	10	Relative and absolute lymphocytosis.
32	7,600	47	44.5	3,572	3,382	17th	30	Relative and absolute lymphocytosis.
33	5,400	36	55	1,944	2,970	4th	9	Slight leucopenia. Relative and absolute lymphocytosis.
34	6,800	40	57.5	2,720	3,904	4th	6	Relative and absolute lymphocytosis.
35	5,800	60	36.5	3,480	2,117	3rd	37	Slight relative lymphocytosis.
36	7,400	41.5	52	3,071	3,848	3rd	9	Relative and absolute lymphocytosis.
37	7,000	42	56	2,940	3,920	3rd	5	Relative and absolute lymphocytosis.
38	13,400	55	36.5	7,370	4,891	8th	8	Leucocytosis. Relative and absolute lymphocytosis.
39	5,600	41	43	2,296	2,408	7th	5	Relative and absolute lymphocytosis.
40	9,000	44.5	43.5	4,005	3,915	4th	4	Relative and absolute lymphocytosis. Slight leucocytosis.
41	6,800	53	40	3,604	2,720	4th	6	Slight relative and absolute lymphocytosis.

REFERENCES.

1. Acker, 'Parotitis with Meningitis,' *Amer. Journ. Obst.*, N. Y., 1913, lxviii. 386.
2. Antonelli, 'Report to Ophthalmol. Sect. of Internat. Med. Congress,' Madrid, 1903, 642, 643.
3. Apert, *Bull. Soc. de Pédiatr. de Paris*, 1907, ix. 233.
4. Barach, 'Morphology of the Blood in Epidemic Parotitis,' *Arch. Int. Med. Chicago*, 1913, xii. 751.
5. Barbieri, 'Pancreatite subacuta e glicosuria, etc.,' *Gazz. degli ospedali*, Milano, 1909, xxx. 273.
6. Blanchard, *Bull. méd.*, Paris, 1899, xiii. 1091.
7. Bloomfield, 'Incubation Period of Mumps,' *Brit. Med. Journ.*, 1905, i. 412.
8. Busquet et Boudeaud, 'Contrib. à l'étude des oreillons du chien,' *Compt. rend. Soc. de Biol. de Paris*, 1900, lii. 675.
9. Busquet et Feri, *Rev. d. Méd.*, Paris, 1896, xvi. 744.
10. Cammidge, *Brit. Med. Journ.*, 1907, ii. 1134.
11. Catrin, 'Quelques obs. sur 159 cas d'oreillons,' *Bull. et Mém. Soc. méd. d'Hôp. de Paris*, 1893, 3^e sér., x. 624.
12. Chauffard et Boidin, 'Deux cas de méningite, etc.,' *Bull. et Mém. Soc. méd. d'Hôp. de Paris*, 1904, 3^e sér., xxi. 477.
13. Chauvin, 'De l'épididymite ourlienne,' Thèse pour M.D. Paris, 1900.
14. Chavanis, *Loire méd.*, St. Étienne, 1891, x. 241.
15. Cheinisse, 'La pancréatite ourlienne,' *La Semaine méd.*, Paris, 1912, xxxii. 85. (With good list of references.)
16. Colomb et Mercier, 'Méningisme ourlien,' *Bull. et Mém. Soc. méd. d'Hôp. de Paris*, 1912, 3^e sér., xxxiii. 240.
17. Comby, 'Néphrite, etc.,' *Union méd.*, Paris, 1893, 3^e sér., lv. 145.
18. Courand et Petges, *Arch. de Méd. mil.*, Paris, 1900, xxxvi. 185.
19. Daireaux, *Bull. méd.*, Paris, 1899, xiii. 227.
20. Dopter, 'Paralysie faciale, etc.,' *Bull. et Mém. Soc. méd. d'Hôp. de Paris*, 1904, 3^e sér., xxi. 912.
21. Dopter, *Progrès méd.*, Paris, 1908, 3^e sér., xxiv. 101.
22. Doudney, *Lancet*, Lond., 1890, ii. 1156.
23. Douglas, *Brit. Med. Journ.*, 1905, i. 594.
24. Dukes, 'The Orchitis of Mumps,' *Lancet*, Lond., 1900, i. 25; *ibid.*, 1906, i. 861.
25. Edgecombe, *Practitioner*, Lond., 1908, lxxx. 194.
26. Feiling, *Lancet*, Lond., 1913, ii. 71.
27. Fichera, 'Ricerche bacteriolog., etc.,' *Bull. d. r. Accad. Med. di Roma*, 1905, xxxi. 29.
28. Findlay, 'Case of Infantile Hemiplegia following Mumps,' *Glasgow Med. Journ.*, 1906, lxv. 50.
29. Freund, 'Beobachtungen, etc., über das Pankreas,' *Wien. med. Woch.*, 1911, lxi. 3134-8.
30. Gallavardin, 'Comp. nerveuses des oreillons,' *Gaz. d'Hôp. Paris*, 1898, lxxi. 1329.
31. Gordon, *Lancet*, Lond., 1913, ii. 275; Reports Local Government Board, New Ser., No. 96, 1914.
32. Graham, 'An Epidemic of Specific Parotitis in School-children,' *Brit. Journ. Child. Dis.*, Lond., 1913, x. 497.
33. Gulland and Goodall, 'Disorders and Diseases of the Blood,' 1912, 25, 67.
34. Harris, 'Case of Diabetes, etc.,' *Boston Med. and Surg. Journ.*, 1899, cxl. 465.
35. Herb, 'Experimental Parotitis,' *Arch. Int. Med. Chicago*, 1909, iv. 201-17.
36. Hirtz, *Bull. et Mém. Soc. méd. d'Hôp. de Paris*, 1901, 3^e sér., xviii.
37. Hirtz and Salomon, 'La phlébite ourlienne,' *Bull. et Mém. Soc. méd. d'Hôp. de Paris*, 1912, 3^e sér., xxxiv. 847.
38. Jaccoud, *Brit. Med. Journ.*, 1885, ii. 41.
39. Jacob, 'A Case of Acute Pancreatitis,' *Brit. Med. Journ.*, 1900, i. 1532.
40. Jones, *Med. Chron.*, Manchester, 1911, liv. 207-11.

41. Joffroy, *Progrès méd.*, Paris, 1886, 2^e sér., iv. 1009.
42. Koplik, *Diseases of Children*.
43. Korentschewsky, *Centralbl. f. Bakteriöl.*, Jena, 1907, Orig. xlv. 394.
44. Krestnikow, Thèse de St.-Petersbourg, 1902.
45. Lacroix, 'Des paralysies périphériques d'origine ourlienne,' Thèse M.D., Bordeaux.
46. Lafforgue, 'Paramyoclonus d'origine ourlienne,' *Rev. de méd.*, Paris, 1912, xxxii. 303-6.
47. Lannois, 'La surdit   ourlienne,' *Lyon m  d.*, 1900, xciii. 469-76.
48. Lannois et Lemoine, *Arch. de Neurol.*, Paris, 1886, xi. 1-15.
49. Laveran et Catrin, 'Recherches bact. sur les oreillons,' *Compt. rend. Soc. de Biol.*, Paris, 1893, 9^e s  r., v. 528.
50. Lefas, *H  matologie et cytologie*.
51. Lemoine et Lapasset, 'Un cas de pancr  atite ourlienne avec autopsie,' *Bull. et M  m. Soc. m  d. d'H  p. de Paris*, 1905, 3^e s  r., xxii. 640.
52. Le Roux, 'Complications oculaires des oreillons,' *Archives d'Ophthalmologie*, Paris, 1903, xxiii. 655-9.
53. Lister and Fearnley, 'Case of Acute Meningitis, &c.,' *Australas. Med. Gaz.*, Sydney, 1905, xxiv. 12.
54. Manine, 'Note sur les oreillons,' *Bull. et M  m. Soc. m  d. d'H  p. de Paris*, 1913, 3^e s  r., xxxv. 1139.
55. Maximowitsch, *St. Petersburg. med. Woch.*, 1880, v. 185.
56. May, 'Complications auriculaires des oreillons,' Th  se de Lyon, 1900.
57. Mearay and Walch, *Med. Record*, New York, 1896, i. 440.
58. Michaelis and Bienn, *Verhandl. des XV^{ten} Congresses f. inn. Med.*, 1897, xv. 441.
59. Miecamp, *Caduc  e*, Paris, 1903, iii. 77.
60. Miller, 'Nephritis complicating Mumps,' *Med. News*, New York, 1905, lxxxvi. 585.
61. Minor, 'Aural Complications in Mumps,' *New York Med. Journ.*, 1897, lxxv. 421.
62. Missimilly, 'Contribution    l'  tude des oreillons chez l'enfant,' Th  se de Montpellier, 1913.
63. Mitchell, *Lancet*, Lond., 1911, i. 23.
64. Monod, Th  se de Paris, 1902.
65. Monro, *Lancet*, Lond., 1883, ii. 280.
66. Nicolle et Conseil, *Compt. rend. Acad. d. Sci. Paris*, 1913, clvii. 340.
67. Nob  court et Br  let, *Bull. Soc. de P  diatr. de Paris*, 1905, vii. 282.
68. Pearse, *Manchester Chronicle*, 1885.
69. Penny, 'The Incubation Period of Mumps,' *Brit. Med. Journ.*, 1904, i. 489.
70. Pick, *Wien. klin. Rundschau*, 1902, xvi. 309.
71. Phillips, *Lancet*, Lond., 1911, i. 23.
72. Poore, *Medical Record*, New York, 1889, xxxv. 543.
73. Raymond, 'La pancr  atite ourlienne,' *Paris m  d.*, 1911-12, ii. 240.
74. R  villiod, *Revue m  d. de la Suisse romande*, Gen  ve, 1896, xvi. 756.
75. Routh, 'Parotitis with Glycosuria and Acidosis,' *Brit. Med. Journ.*, 1912, ii. 64.
76. Roux, 'Les m  ningites ourliennes,' *Gaz. des H  p.*, Paris, 1914, lxxxvii. 549.
77. Roy, *Bull. m  d.*, Paris, 1907, xxi. 313.
78. Sacqu  p  e, 'Formule h  moleucocytaire des oreillons,' *Arch. de M  d. exp  r. et d'Anat. path.*, Paris, 1902, xiv. 114.
79. Sen, *Indian Med. Gaz.*, 1909, xlv. 98.
80. Sicard, *Bull. et M  m. Soc. m  d. d'H  p. de Paris*, 1905, 3^e s  r., xxii. 135.
81. Sicard, 'Hydroc  phalie acquise par m  ningite ourlienne,' *Revue neurol.*, Paris, 1914, xxvii. 706.
82. Sicard et Dopter, *Compt. rend. Soc. de Biol.*, Paris, 1905, lviii. 317.
83. Simonin, 'Thyroidite et thyroidisme dans l'infection ourlienne,' *Bull. et M  m. Soc. m  d. d'H  p. de Paris*, 1901, 3^e s  r., xviii. 374.
84. Simonin, 'La pancr  atite ourlienne,' *ibid.*, 1903, 3^e s  r., xx. 928.
85. Talon, *Arch. de M  d. et Pharm. mil.*, Paris, 1883, i. 103.
86. Teissier et Esmein, *Compt. rend. Soc. de Biol.*, Paris, 1906, lx. 803, 853.
87. Thomson, *Arch. Pediatr.*, New York, 1897, xiv. 603.

88. Torpey, *Journ. Amer. Med. Assoc.*, Chicago, 1911, lvi. 742.
89. Tresilian, 'A Sign of Mumps,' *Brit. Med. Journ.*, 1901, i. 889.
90. Troussaint, *Arch. de Méd. et Pharm. mil.*, Paris, 1893, xxii. 332.
91. Trousseau, *Lectures on Clinical Medicine*. (New Sydenham Society.) Vol. i, Lecture xi.
92. Voss, 'Zur Ätiologie der Erkrankungen des inneren Ohres bei Parotitis epidemica,' *Zeitsch. f. Ohrenh., etc.*, Wiesb., 1914, lxx. 58.
93. Waddelow, 'Primary Epididymitis in Mumps,' *Brit. Med. Journ.*, 1909, i. 1480.
94. Warrington, *Liverpool Med. Chir. Journ.*, 1914, No. 65.
95. Wile, 'The Blood Changes in Mumps,' *Arch. Pediatr.*, New York, 1906, xxii. 669.
96. Woodward, 'The Ocular Complications of Mumps,' *New York Med. Journ.*, 1904, lxxix. 20; *ibid.*, 1907, lxxxv. 123.
97. Zade, 'Ein Beitrag zur Polymorphie der Paulitis epidemica, etc.,' *Arch. f. Kinderh., Stuttg.*, 1912, lvii. 261.
98. *Report of Committee appointed by Clinical Society*, Supplement to vol. xxx, 1892.

THE PITUITARY GLAND IN DIABETES MELLITUS AND DISORDERS OF THE GLANDS OF INTERNAL SECRETION

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With Plates 13 and 14

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Introduction.

THE correlation which has been found to exist between the various glands of internal secretion makes it important to ascertain whether any changes occur in the remaining glands in cases of primary disease of one of the series. The pituitary body was the main object of investigation in the present instance, since data are still insufficient with reference to the changes occurring in this organ in certain diseases of the glands of internal secretion.

In the case of diabetes mellitus in particular no systematic investigation of the pituitary gland appears to have been made. Since Goetsch, Cushing, and Jacobson (1) have shown that the posterior lobe of the pituitary body plays an

important part in carbohydrate metabolism, it seemed possible that definite histological changes might be present in this organ in cases of diabetes mellitus. Moreover Weed, Cushing, and Jacobson (2) have recently found that electrical stimulation of the pituitary gland itself causes glycosuria, even when all paths of conduction of nervous impulses to the abdominal organs have been interrupted. That changes in the pituitary gland might in some cases be directly related to glycosuria appeared not improbable, in view of the fact that in many cases of diabetes mellitus no histological changes in the pancreas are found.

Attention was therefore directed particularly to glycosuria and to diseases of the pancreas. At the same time certain other diseases of internal secretion were investigated with the hope of throwing some additional light upon the functions of the pituitary body and its relation to other organs of internal secretion.

1. *Removal* of the pituitary was effected by cutting through the diaphragma sellae between the anterior and posterior clinoid processes on both sides and between the anterior clinoid processes in front, and dividing the dorsum sellae behind with chisel and bone forceps. With very little dissection along its anterior border the pituitary gland could then be removed from the body without any damage to the organ while lodged in its bony compartment. It was then immediately placed, still lying *in situ*, in the fixative.

2. *Fixation* was performed by Formol-Muller's fluid and salt formalin solution. The organ was first fixed for twelve to twenty-four hours in salt formalin solution. It was then easily dissected from its bony chamber without injury and adherent tissues removed. The organ was gently dried and then weighed. After weighing it was bisected with a sharp razor accurately in the antero-posterior mesial plane.

Microtome sections were made as close as possible to the mesial plane.

3. *Staining*. The stains used were haemalum and eosin, Leishman or Giemsa for routine examination, and for special purposes van Gieson and Gram-Weigert.

I. Diseases of Pancreas. A. Diabetes Mellitus.

Name.	Sex.	Age.	Cause of Death.	Body Weight in kilos.	Pituitary. grm.	Pancreas. grm.	Thyroid. grm.	Ratio of Pituitary to Body Weight.
1. K. S.	F.	29	Diabetes	—	0.65	22.5	—	
2. M. H.	F.	32	Diabetes	30.15	0.45	70	—	$\frac{1}{67000}$
3. B. G.	F.	40	Cholelithiasis. Sub-diaphragmatic abscess. Diabetes	—	0.72	100	—	
4. H. T.	M.	53	Appendix abscess. General peritonitis. Diabetes	—	0.65	100	—	
5. G. K.	M.	14	Diabetes. Coma	—	—	—	—	
6. H. K.	M.	31	Diabetes. Coma	52.9	0.6	50	—	$\frac{1}{88100}$
7. P. H.	F.	35	Pregnancy. Diabetes. Coma	—	0.52	60	—	
8. J. S.	M.	43	Diabetes. Coma	44.1	1.16	72	30	$\frac{1}{38000}$

Summary of Characters of Pituitary Gland in Diabetes. (See Appendix.)

The *cut surface* sometimes shows a wide interglandular cleft. White homogeneous irregular areas may be present in the anterior lobe. The upper border of the gland is flattened or concave. The anterior lobe is diminished in size.

The average *weight* is about 0.63 gm., which falls within the limits of the average weight of the gland in adults. The low weight recorded in Case 2 may be accounted for by damage in removal, while in Case 8, which had the highest recorded weight, 1.16 gm., there was an abscess involving the anterior lobe.

The cells of the *anterior lobe* are usually eosinophilic, rarely basophilic (No. 6). The eosinophilic cells are grouped chiefly towards the posterior end of the lobe, though they may be scattered throughout the whole lobe. Chief cells are usually present in moderate amounts mainly at the periphery of the lobe. Frequently they show well-marked transition stages into eosinophilic cells. The features of chief interest are the marked increase of the chromophil cells, often forming definite adenomatous masses, and the active transference of the cells of the eosinophilic, and to a less extent of the basophilic variety, into colloid, with the result that colloid invades the posterior part of the anterior lobe and may extend far into its centre (Cases Nos. 1 and 4) (*vide* Plate 13, Figs. 1 and 3). Small masses of colloid may be seen in the centre of a number of cells grouped in an alveolar manner with granules (Cases Nos. 1, 3, and 5) clustered at the free alveolar border of the cells (*vide* Plate 13, Fig. 2), as in a rapidly secreting gland. The conversion of cells into granular material may occur without formation of the ordinary colloid masses. The free granules and granules in the cells are highly refractile and sometimes golden in appearance, very similar to those seen in the posterior lobe. The colloid itself can often be seen to be finely granular, and at the periphery granular masses can be seen in direct continuity with colloid, in the midst of which lie small clumps of chromophil cells and isolated nuclei (Plate 13, Fig. 3). The reaction of the colloid is eosinophilic or basophilic according to the preponderance of the type of chromophil cell in relation to it. Areas of cellular necrosis are present in the anterior lobe in four cases (Nos. 2, 5, 7, and 8) (Plate 13, Figs. 4 and 5, and Plate 14, Fig. 7). These areas are situated towards the posterior end of the anterior lobe and may abut on the interglandular cleft. Their size is variable. They may be quite small (No. 2) (Plate 13, Fig. 4), or may involve a large part of the anterior lobe (Nos. 7 and 8) (Plate 13, Fig. 5, and Plate 14, Fig. 7), so that few of its cellular elements remain. Their outline is irregular and there is no sharp line of delimitation between the normal cells of the lobe and these areas of necrosis. The delicate fibrous and connective-tissue meshwork of the lobe remains intact, in the interstices of which may be seen rounded nuclei, cells in varying stages of degeneration, and small masses of colloid. The blood-vessels in these areas are intact and contain red cells. As a rule no micro-organisms can be detected by staining methods in these areas.

The texture of the lobe as a whole is usually compact, rarely loose. Occasionally there appears to be an increase of connective tissue, indicating a fibrosis (Nos. 4 and 7). Blood-vessels frequently contain small colloid masses.

Cells in the *pars intermedia* may be either eosinophil or basophil. The interglandular cleft is sometimes widely distended, and contains much colloid, as a rule mingled with cells and nuclei (Nos. 1 and 2). At other times, though the cleft may be wide, it only contains a little thin granular colloid, or none at all. Collections of nuclei are frequently present in such cases (No. 6). The reaction of the colloid varies in a similar manner to that in the anterior lobe.

In the *pars posterior* golden granules are numerous as a rule. In some cases large cells lying in the nervous tissue are filled with these granules, so that only the nucleus is visible (No. 1). In other cases they appear to be lying free in the meshwork of the lobe. Transition stages can be seen between these granules and finely granular small masses of colloid, staining freely with eosin. In the cases in which the granules are numerous colloid masses are sometimes less evident. Invasion of the anterior border of the posterior lobe by cells, usually basophilic, is sometimes noticeable.

The chief cells clothing the *stalk* show widely dilated cystic spaces, containing colloid in a few instances. Colloid is usually present in masses of varying size. The nervous portion of the stalk always contains small colloid masses.

Character of changes. Definite histological changes therefore occur in the anterior lobe of the pituitary in cases of diabetes and glycosuria. These changes are represented by (1) an increase in the chromophil cells, (2) conversion of chromophil granular cells into colloid or granular masses, and (3) areas of degeneration which may be of such a size that few of the cellular elements remain in the anterior lobe (Cases 7 and 8). It is possible that these changes may be independent of one another, but it is suggested that they are directly connected in the following manner :

Relation of changes to one another. The conversion of granular cells into colloid in the anterior lobe has already been mentioned and has been noted by many authors, Comte (5), Cagnetto (12), and others. This colloid passes into the interglandular cleft, with the colloid of which it is directly connected. If this colloid which infiltrates the posterior border of the anterior lobe becomes absorbed it leaves the area which it occupied denuded of cells, only the connective-tissue framework remaining. This explanation of the formation of these areas of degeneration is supported by the fact that small masses of colloid can still be seen in the connective-tissue meshwork of these areas. Moreover, nuclei and granular degenerated cells, which show all stages of transition from the normal epithelial elements of the lobe, are also present. Further, at the periphery of these areas, there is no sharp boundary zone, and the tissue meshwork passes insensibly into the normal cellular tissue of the lobe. The extreme vascularity of the anterior lobe and the normal appearance of the vessels seem to exclude the formation of these areas by an interference with the vascular

supply of the part. Their situation at the posterior end of the anterior lobe is in the position in which chromophil cells are most numerous and colloid formation most active. In Case 8, in which a gummatous deposit lay over the infundibulum at the base of the brain, an interference with the blood supply to the anterior lobe is conceivable, especially as almost the whole of the anterior lobe had undergone degeneration, with the exception of the linguiform portion and the posterior portion of the anterior lobe, which would receive a collateral circulation from the region of the pars intermedia. In this connexion it is of interest to note that Cushing (20) quotes a case diagnosed as pancreatic diabetes in which a syphiloma was found involving the pars anterior and pars intermedia. That injuries to the head, especially fractures of the base, are frequently associated with glycosuria, has been the subject of comment (Nothnagel, Cushing). In these cases injury to the pituitary body is not unusual, often with haemorrhages into its substance (Cushing, 20). It appears, therefore, that lesions of the pituitary body can be the primary cause of a glycosuria. This is substantiated by the recent work of Weed, Cushing, and Jacobson (2). The adenomatous formations of chromophil cells seen in Case 4 are very similar to those described by Lewis (21) and Benda as occurring in the anterior lobe of the pituitary body in cases of acromegaly. The frequent occurrence of diabetes with acromegaly, especially in the earlier stages of the latter, is well known. These adenomatous formations may, therefore, be the expression of a primary functional change in the pituitary directly related to glycosuria. The increased formation of colloid in the posterior part of the anterior lobe (*vide* Plate 13, Figs. 1 and 2) has been shown to be a direct sequence to these adenomatous formations. Schäfer (22) found an increased formation of colloid in the pars intermedia in dogs whose infundibulum had been injured by means of a cautery, and these animals exhibited a marked polyuria. A similar result was obtained by Cushing and Goetsch (23) after placing a clip upon the stalk of the pituitary. They found a hyperplasia of the cells of the pars intermedia and increase of the hyaline and granular bodies. They state, however, that they were unable to find the colloid in the interglandular cleft endowed with the active principles of extracts of the posterior lobe. They admit that this is surprising, since they consider the hyaline bodies to be derived from the cells of the pars intermedia, and these are a part of the anterior lobe. It is possible that the colloid in its passage through the posterior lobe may become activated, or perhaps modified by some secretion of the posterior lobe. On this theory, the removal of the major part of the anterior lobe, which is followed after a primary glycosuria by increased sugar tolerance, as found by Cushing, Crowe, and Homans (24), would be due to removal of potential secreting cells.

Relation of changes to severity of disease. The differences in the character of the changes do not appear to be related to the duration of the diabetes, since in all the cases the history of the disease was one year or more. The severity of the glycosuria and of the disease, however, appears to be reflected in the changes in the pituitary. Thus, in Case 3 the amount of sugar in the urine was

small and was readily controlled by a diabetic diet. Here the adenomatous masses of eosinophilic cells are evident, but little colloid formation is present. The same may be said of Case 4. On the other hand, in Case 1, in which sugar excretion was high and death occurred rapidly, the colloid invasion of the anterior lobe is very marked. In Case 7, in which the patient suddenly went into coma and died within twenty-four hours, an extensive area of necrosis is present in the anterior lobe. In Case 8, in which the sugar excretion had been very great and the history prolonged, the degeneration affects almost the whole of the anterior lobe. That these areas of necrosis and the other changes mentioned are not merely unconnected secondary effects of the disease, such as the cystic degenerations in the brain described in diabetes, is shown by the fact that no degenerative changes are present in the posterior lobe, which would be more likely to experience such changes.

Relation of Changes to other Ductless Glands.

Next must be considered whether the changes above described are secondary effects due to some interrelation between the pituitary and the pancreas. In only four out of the eight cases examined were histological changes demonstrable in the pancreas, and in only two out of these four were the changes in any way well marked. In Case 2 the islets of Langerhans were very remarkable both for their number and size, forming indeed almost adenomatous masses. They showed further the hyaline degeneration upon which stress has been laid by Opie (25), with an interacinar fibrosis. In Case 8 were present the large areas of fibrosis and formation of new ducts which were described by Saundby. Two other cases (1 and 3) showed a slight degree of chronic inflammation and fibrosis. In 50 per cent. of the cases, however, there were no gross histological changes demonstrable. It is true that the usual method of examination of the pancreas by means of samples is open to objection, as has been shown by Bensley (26), who found considerable differences in the number of islets in closely adjacent regions. It must also be admitted that Bensley fixation and staining methods for the demonstration of cell granules of the pancreas were not undertaken. In view of the fact that the material was obtained from the post-mortem room, these methods did not appear likely to be of value. Apart from these considerations, in half the cases examined no gross histological lesions were demonstrable in the pancreas, and this is in accord with the findings of most investigators (Biedl).

There appears to be no correlation between the presence or severity of the histological changes in the pancreas and the character of the changes present in the pituitary body, nor in the cases examined is there any connexion between the severity or duration of the diabetic condition and the presence of pancreatic lesions.

The clinical symptoms did not differ in any marked way in any of the cases examined, except in Case 8, in which headache was a prominent feature, possibly

due to the marked changes in cerebral vessels and meninges. The Wassermann reaction was performed in only one case (No. 2), and in that case was negative.

The thyroid gland was examined in five out of the eight cases, and in four out of the five cases the histological appearance was normal. In one case (No. 7) there was atrophy of the alveoli and diminution of the colloid with proliferation of the cells lining the alveoli, round-celled infiltration, and fibrosis (*vide* Plate 14, Fig. 6). It is difficult to say whether these changes were due wholly or in part to the condition of pregnancy which complicated the diabetes. It must be noted, however, that a large area of necrosis was present in the anterior lobe of the pituitary, and less than a third of its normal cellular elements remained. In this case the histological picture of the thyroid exactly resembles that depicted by Cushing (20) as present in the thyroid of dogs after total hypophysectomy. It may be that the changes are directly connected and that the thyroid acts in sympathy with the anterior lobe of the pituitary.

The parathyroid glands were examined in one case, No. 6, and found to be normal. There was a slight alveolar arrangement of the cells with colloid formation at one point. The thyroid gland in this case was normal.

B. *Acute Pancreatitis.*

Name.	Sex.	Age.	Weights of Organs.	
			Pancreas. gm.	Pituitary. gm.
1. W. R.	M.	33	190	0.6
2. L. B.	M.	50	260	0.68
3. A. T.	F.	78	—	0.69

C. *Carcinoma of Pancreas.*

1. T. L.	M.	56	—	0.5
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Summary of Characters of Pituitary Gland in Diseases of Pancreas.

(See Appendix.)

B. Acute Pancreatitis. Cut surface, The anterior lobe shows no diminution in size, and the upper border is not concave.

Weight is within normal limits, except in the case of the carcinoma of pancreas, in which the weight is low. There was, however, considerable wasting of the body generally.

The anterior lobe shows but little increase in the number of eosinophilic cells, and the bulk of it is composed of the ordinary chief cells. Basophilic cells are not numerous. There is, however, a slight but usually definite increase in the amount of colloid present as small masses throughout the lobe, surrounded by an alveolar arrangement of cells. There may be a slight invasion of the posterior end of the anterior lobe by colloid.

Pars intermedia. Colloid is usually present in considerable amount. The granular character of the colloid is noticeable.

Pars posterior. Golden granules are conspicuous, and as a rule colloid masses can be seen towards the region of the interglandular cleft.

C. Carcinoma of Pancreas. The gland shows some general diminution in size.

Anterior lobe. The characters are those of a normal gland except for the diminution of the cellular elements and increase of interstitial tissue.

Pars intermedia. Colloid formation is slight or absent.

Pars posterior. Golden granules are very prominent.

In the above cases, in which there was very great, and in the case of carcinoma of pancreas almost total destruction of the pancreas, the histological changes in the pituitary are very slight. Granular pigment masses and hyaline bodies are, however, more noticeable in the pars nervosa in the vicinity of the pars intermedia. Especially the pigment granules are more numerous than in the normal gland, and in the case of carcinoma of pancreas are very striking. Cushing and Goetsch (23) found an increase of the granular and hyaline bodies in the posterior lobe and infundibulum after extirpation of the pancreas in dogs. The occurrence of diabetes in subjects who have survived an attack of acute pancreatitis and in cases of carcinoma of pancreas has been sometimes observed. But, as a rule, in the former death ensues so rapidly that it would seem unlikely that marked changes would occur in the pituitary.

II. Diseases of Thyroid.

A. Myxoedema.

Name.	Sex.	Age.	Body Weight in Kilos.	Ratio of Pituitary to Body Weight.	Thy- roid.	Pitui- tary.	Thy- mus.	Pan- creas.	Ad- renals.	Ovaries.
					gm.	gm.		gm.	gm.	gm.
1. J. W.	F.	47	—	—	4	0.95	—	110	39	+ uterus and appendages 150
2. K. W.	F.	46								

B. Hypertrophy. Cystic Goitre.

3. M. F.	F.	18	54.59	1/8000	left lobe re- moved	0.7	50	90	13	right 4 1/2 } 12 1/2 left 8 }
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Summary of Characters of Pituitary in Diseases of Thyroid Gland.

(See Appendix.)

A. Myxoedema. Cut surface. The anterior lobe is much increased in size in all directions, and is about double the size of the posterior lobe. Its consistency is firmer than usual and its appearance tough and fibrous and of dark reddish colour.

The weight is considerably above the normal in Case 1. Unfortunately, in Case 2 no weight was recorded, but the gland showed much enlargement.

In the first instance the weight is comparable to that of the hypertrophied gland in pregnancy, even of multipara, and is about double the average weight of the normal gland in adults. Former investigations of the pituitary gland in myxoedema are somewhat contradictory. Schönemann (27) found after thyroid extirpation with subsequent myxoedema increase in weight of the gland. Boyce

and Beadles (28) noted hypertrophy of the organ in myxoedema, and this was the finding of Comte (5) and most subsequent investigators, though Ponfick (29) found degeneration of the pituitary but does not record its weight. Increase in weight of the pituitary after thyroidectomy has been recorded by numerous investigators, of whom the most recent is Degener (30).

The anterior lobe is composed mainly of chief cells, which are present in large numbers, closely packed together and with basophilic protoplasm. It is to their increase that the enlargement of the anterior lobe is due. Basophilic cells are numerous and greatly preponderate over the eosinophilic, which are remarkably few. A noticeable feature is the presence of large amounts of colloid in the interstitial spaces and in the blood-vessels or in alveoli. Degenerated cells with vacuolated clear protoplasm are numerous and masses of granular material (Plate 14, Fig. 8). There is an increase of the interstitial fibrous tissue.

Pars intermedia. Colloid formation is very marked, and is contained in large dilated alveoli. Colloid is usually basophilic, sometimes eosinophilic. The transformation of cellular protoplasm into colloid is noticeable. Colloid is also in evidence at the base of the stalk.

Pars nervosa. The golden granules are numerous, but colloid masses are not marked. The neuroglial network seems to be closer in texture and more granular in appearance. The stalk also shows the same granularity in its nervous portion.

B. Goitre. Cut surface. The anterior lobe shows no enlargement and is of normal appearance.

Weight is slightly in excess of the average weight of the normal gland in the second decade.

The anterior lobe. Great increase of the eosinophilic cells is noticeable, while other cell forms are few. The eosinophilic cells are large, closely packed together, and filled with granules.

Pars intermedia. Colloid formation is present in considerable quantity.

Pars posterior. Golden granules are few, but hyaline bodies are numerous and pale round granular bodies are present in large numbers throughout the lobe and in the nervous portion of the stalk.

Comparing the histological appearance of the pituitary body in myxoedema and goitre, a striking contrast is evident, which explains the differences in the naked-eye characters of the two glands. The cells forming the anterior lobe are mainly chief cells in myxoedema, while eosinophils are predominant in goitre, and this contrast between the eosinophilic appearance of the anterior lobe in goitre and its basophilic character in myxoedema is very definite. Further, in goitre the cells are closely packed, large, with abundant protoplasm richly granulated. In myxoedema, on the other hand, large cells with vacuolated poorly staining protoplasm and large masses of granular debris are evident, which indicate an exhausted condition of the anterior lobe. These appearances no doubt give a clue to the functional activity of the gland in the two conditions, vegetative and of low activity in myxoedema, highly active in goitre. On the other hand, in spite of the physiological atrophy of the gland, there is an anatomical hypertrophy of

the organ in myxoedema due to the increase of fibrous tissue in the anterior lobe, and multiplication of chief cells. It is worthy of remark that in Case 7 of the diabetic series, in which there was a large area of degeneration in the anterior lobe of the pituitary body, the thyroid showed histological changes almost identical with those in a myxoedematous gland (cf. Plate 14, Fig. 6). Cushing (20), moreover, has found similar changes in the thyroid after hypophysectomy. The considerations above mentioned support the findings of Schönemann (27), who noted hyaline degeneration of the stroma and atrophy of the gland, but an increase in weight. Comte (5) found a large amount of colloid in the interglandular cleft, and in the anterior lobe numerous small intra-acinar masses of colloid and abundant chromophobe cells, but the cyanophils were more numerous than the eosinophils. Abrikossoff (31) found hypertrophy due to increase of stroma and colloid and increase of acidophils. McCallum and Fabyan (32), in a careful study of the pituitary of a cretin, noted abundance of cyanophils and in general give a description which exactly corresponds with that recorded here. After experimental thyroidectomy both Rogowitsch (33) and Stieda (34) found an increase of the chief cells in the pituitary. Herring (9) after thyroidectomy in cats found no changes in the anterior lobe of the pituitary four to six days later, but there was granularity of the nervous substance and an increase in the hyaline and granular bodies in the pars nervosa, but no increase of colloid in the interglandular cleft. These results are perhaps explicable by the short lapse of time between the thyroidectomy and the histological examination.

In goitre the marked hyperplasia of eosinophilic cells, abundant colloid in the interglandular cleft, with the remarkable amount of granular bodies in the infundibulum, all indicate a gland in a high degree of activity. In goitre Schönemann (27) found increase in the chromophils, especially of the eosinophils, and increase of colloid. Cushing and others have noted in acromegaly, in which adenomata of eosinophilic cells are commonly found in the anterior lobe, that enlargement of the thyroid occurred. Comte (5) in goitre observed a greater increase in the eosinophils than in the cyanophils, and an increase of colloid in the interglandular cleft. It must be noted that the colloid of the intraglandular cleft in myxoedema, though increased in amount, is more vacuolated, thinner, and more granular, often more basophilic in reaction than is the case in goitre. The presence of numerous masses of hyaline bodies in the posterior lobe and few granules in goitre contrasts strongly with the condition in myxoedema in which golden granules are numerous and hyaline bodies few.

In all its histological features, therefore, the pituitary in goitre stands opposed to that in myxoedema, and it would seem that the pituitary does not, as has been sometimes claimed, function vicariously with the thyroid, but responds in the same direction as that gland to the biochemical stimuli which influence it.

In spite of the well-marked degeneration of islets of Langerhans in J. W. (Case I) there was no clinical evidence of diabetes. Vacuolization of the cells of the cortex of the adrenals was noted in both cases of myxoedema, a feature which Cushing (20) has observed in cases of hypopituitarism. The

ovaries in the cases of myxoedema and of goitre showed as marked histological contrasts as did the thyroid glands. The enormous hypertrophy of lutein cells and large colloid cysts in the case of goitre indicated heightened glandular activity as markedly as the great fibrosis and absence of glandular tissue in the cases of myxoedema indicated lowered function. The three organs, pituitary, thyroid, and ovary, appear to be influenced in a similar manner.

III. *Diseases of Adrenals. Addison's Disease.*

Name.	Sex.	Age.	Body Weight.	Ratio of Pituitary to Body Weight.	Pituitary.	Adrenals.	Thyroid.	Pancreas.
					gm.	gm.	gm.	gm.
W. McG.	M.	18	—	—	0.45	22	22	40

The pituitary body in this case presents no outstanding features. The histological picture suggests perhaps a gland in a low degree of functional activity. This is remarkable in view of the fact that extirpation of both adrenals is followed by hypertrophy of the anterior lobe of the pituitary according to Marengi (35); no systematic histological examination of the pituitary gland in Addison's disease appears to have been made.

IV. *Diseases of Thymus. Hypertrophied Thymus.*

Name.	Sex.	Age.	Cause of Death.	Pituitary.	Thymus.	Testicles.
				gm.	gm.	gm.
W. W.	M.	1½ yr.	Operation for undescended testicle. Status thymo-lymphaticus.	0.16	30	Left 3.15 Right 2.37

The pituitary in this case presents no peculiar features. Cushing (20), however, quotes two cases of death due to status thymo-lymphaticus. In one case there was a large pituitary tumour which had deformed the surrounding structures. The growth was formed of masses of neutrophilic chromophobe chief cells, and he regards the case as one of primary hypophysial deficiency. The other case was an internal hydrocephalus due to a gliomatous cerebellar cyst. The pituitary body showed a large colloid cyst in the pars intermedia and there was hyperplasia of the pars intermedia. Cushing interpreted the case as one of hypopituitarism due to obstruction to the hypophysial secretion.

The only evidence for hypopituitarism in the present instance was the absence of colloid in the pars intermedia and absence of hyaline and granular bodies. The case of goitre described in the thyroid series presented many of the features of a status thymo-lymphaticus, and in this instance there was marked hyperfunction of the pituitary and ovaries. The non-descent of the right testicle and the poor development of glandular tissue in the present case may be connected with the enlarged thymus, since there is stated to be a close relation between this organ and the reproductive glands. Hewer (36) has

recently found that excessive thymus feeding causes degenerative changes in the testes and sterility, while in the reverse direction castration causes increased weight and retarded atrophy of the thymus (Henderson, Calzolari).

Summary.

1. Definite histological changes occur in the anterior lobe of the pituitary in cases of diabetes in the form of adenomatous masses of eosinophilic cells, colloid invasion of the anterior lobe, and areas of cellular degeneration.
2. Histological changes in the pituitary are absent or slight in cases of acute pancreatitis and carcinoma of pancreas.
3. Increase in weight of the pituitary occurs in myxoedema due to increase of connective-tissue elements and hyperplasia of chief cells.
4. In goitre there is hyperplasia of the chromophil cells, especially of the eosinophilic granular cells, and increase of colloid in the interglandular cleft.
5. No histological changes were observed in the pituitary gland in a case of Addison's disease or in a case of status thymo-lymphaticus.

Conclusions.

The following conception of the activity and mode of secretion of the gland is tentatively suggested:

The eosinophilic and basophilic granular cells are derived from the chief cells by formation of zymogen granules. The granular cells represent a stage of active secretion, and glandular activity is greater towards the centre and posterior border of the anterior lobe. Colloid is formed from the granules. The interglandular cleft serves as an alveolus for the temporary storage of colloid. In conformity with the upward and backward direction of development of the anterior lobe, whereby it becomes attached to the posterior lobe and infundibulum, the colloid secretion passes into the posterior lobe and up into the infundibulum and gains access to the cerebro-spinal fluid. The hyaline and granular bodies are derived from cells of the anterior lobe which have been carried into the substance of the posterior lobe in the process of development. It is upon these cells that the call for increased secretory activity first falls. Colloid in the interglandular cleft is then utilized, and, if there is an over-demand upon the secretory activity of the anterior lobe, colloid may invade the posterior part of the anterior lobe and the cells themselves become rapidly converted into colloid, until finally areas of atrophy of the cells appear. Whether the posterior lobe activates the colloid in its passage or adds some specific secretion of its own, or merely acts as an indifferent supporting structure, must be left undecided.

REFERENCES.

1. Goetsch, Cushing, and Jacobson, *Johns Hopkins Hosp. Bull.*, Baltimore, 1911, xxii. 165.
2. Weed, Cushing, and Jacobson, *ibid.*, 1913, xxiv. 40.
3. Erdheim und Stumme, *Ziegler's Beitr. z. path. Anat.*, Jena, 1909, xlv. 1.
4. Schönemann, *Virch. Arch. f. path. Anat. u. Physiol.*, Berlin, 1892, cxxix. 318.
5. Comte, *Ziegler's Beitr. z. path. Anat.*, Jena, 1893, xxiii. 90.
6. Huie, *Quart. Journ. Microscop. Sci.*, Lond., 1897, N. S. xxxix. 387.
7. Saint-Remy, *Arch. de Biol.*, Liège and Paris, 1892, xii. 425.
8. Benda, *Arch. f. Anat. u. Physiol.*, Leipzig, 1900, *physiol. Abt.*, 373; *Berl. klin. Woch.*, Lond., 1900, xxxvii. 1205.
9. Herring, *Quart. Journ. Exp. Physiol.*, Lond., 1908, i. 121 et seq.
10. Gemelli, *Arch. per le sci. med.*, Torino, 1906, xxx. 521.
11. Scaffidi, *Arch. f. mikros. Anat. u. Entwickl.*, Bonn, 1904, lxiv. 235.
12. Cagnetto, *Virch. Arch. f. path. Anat. u. Physiol.*, Berlin, 1904, clxxvi. 115.
13. Neubert, *Ziegler's Beitr. z. path. Anat.*, Jena, 1909, xlv. 38.
14. Schnitzler und Ewald, *Wien. klin. Woch.*, 1896, ix. 657.
15. Wells, *Journ. Biol. Chem.*, Baltimore, 1909-10, vii. 259.
16. Denis, *ibid.*, 1911, ix. 363.
17. Simpson and Hunter, *Quart. Journ. Exp. Physiol.*, Lond., 1910, iii. 121; *ibid.*, 1911, iv. 257.
18. Kohn, *Arch. f. mikros. Anat. u. Entwickl.*, Bonn, 1910, lxxv. 337.
19. Erdheim, *Sitzungsab. d. k. Akad. d. Wissensch.*, Wien, 1904, Abt. 3, cxliii. 537.
20. Cushing, *The Pituitary Body and its Disorders*, Philadelphia, 1912.
21. Lewis, *Johns Hopkins Hosp. Bull.*, Baltimore, 1905, xvi. 157.
22. Schäfer, *Proc. Roy. Soc.*, Lond., 1909, Ser. B, lxxxi. 442.
23. Cushing and Goetsch, *Amer. Journ. Physiol.*, 1910-11, xxvii. 60.
24. Crowe, Cushing, and Homans, *Johns Hopkins Hosp. Bull.*, Baltimore, 1910, xxi. 127.
25. Opie, *Journ. Exper. Med.*, New York, 1901, v. 397.
26. Bensley, *Amer. Journ. Anat.*, 1911-12, xii. 297.
27. Schönemann, *Virch. Arch. f. path. Anat. u. Physiol.*, Berlin, 1892, cxxix. 318.
28. Boyce and Beadles, *Journ. Path. and Bact.*, Edinb., 1893, i. 223.
29. Ponfick, *Zeitsch. f. klin. Med.*, Berlin, 1899, xxxviii. 1.
30. Degener, *Quart. Journ. Exp. Physiol.*, Lond., 1913, vi. 111.
31. Abrikossoff, *Virch. Arch. f. path. Anat. u. Physiol.*, Berlin, 1904, clxxvii. 426.
32. McCallum and Fabyan, *Johns Hopkins Hosp. Bull.*, Baltimore, 1907, xviii. 341.
33. Rogowitsch, *Ziegler's Beitr. z. path. Anat.*, Jena, 1889, iv. 455.
34. Stieda, *ibid.*, 1890, vii. 534.
35. Marengi, *Biochem. Centralbl.*, Leipzig, 1904, ii. 152.
36. Hewer, *Journ. Physiol.*, Camb., 1913-14, xlvii. 479.

DESCRIPTION OF PLATES.

Microphotographs, Figs. 1, 3, 4, 5, 7, with Leitz's Ocular 2, Objective 3.
 " " 2, 8, 9 " " " 3, " $\frac{1}{2}$ oil immersion.
 " " 6 " " " 3, " 6.

PLATE 13, FIG. 1. Pituitary gland, anterior lobe. Incipient diabetes, Case 4. Adenomatous mass of eosinophilic cells (dark) at posterior end of anterior lobe. Masses of colloid in alveoli and invading the cells of anterior lobe.

FIG. 2. The same. Adenomatous area enlarged, showing the eosinophilic cells with border towards acinus crammed with eosinophilic granules. Basal half of cells clear. Colloid in centre of acinus.

FIG. 3. Pituitary gland, anterior lobe and interglandular cleft. Diabetes, Case 1. Large mass of colloid invading the posterior end of anterior lobe with rapid conversion of granular cells into colloid. Clumps of granular chromophil cells and nuclei lying amid the colloid.

FIG. 4. Pituitary gland, anterior lobe and interglandular cleft. Diabetes severe. Clear area of degeneration of cells surrounded by normal cells.

FIG. 5. Pituitary gland, anterior lobe. Pregnancy and severe diabetes, Case 7. Large area of cellular necrosis (left), degenerating cells in alveoli (right).

PLATE 14, FIG. 6. Thyroid gland. Same case. Diabetes and pregnancy, Case 7. Diminution of colloid, hyperplasia and desquamation of lining epithelium of alveoli. Round-celled infiltration and fibrosis.

FIG. 7. Pituitary gland, anterior lobe. Diabetes severe, Case 8. Atrophy and degeneration of cells (above), cells of anterior lobe invaded by polymorphonuclear cells (below). Suppurating gumma of anterior lobe.

FIG. 8. Pituitary gland, anterior lobe. Myxoedema (Case 1), Thyroid series. Chief cells with clear finely granular protoplasm and indefinite outline surrounding an alveolus containing colloid. Proliferation and massing together of chief cells.

FIG. 9. Pituitary gland, anterior lobe. Cystic goitre. Closely packed masses of large finely granular eosinophilic cell. Cell outlines defined. No colloid.

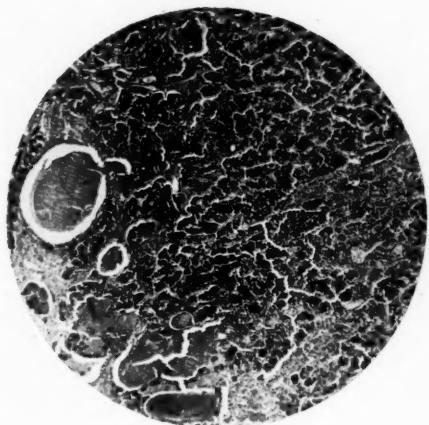


FIG. 1

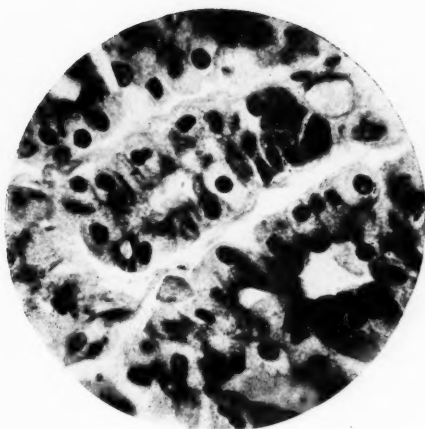


FIG. 2

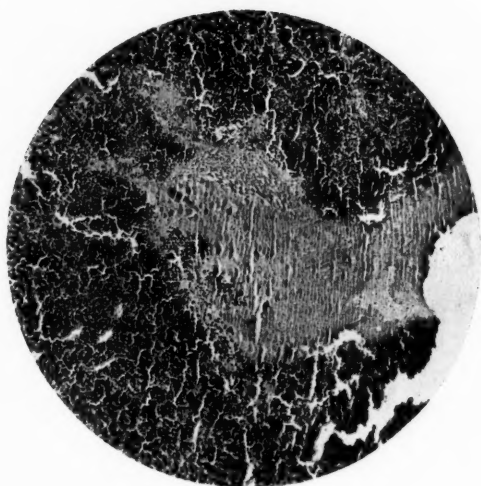


FIG. 3

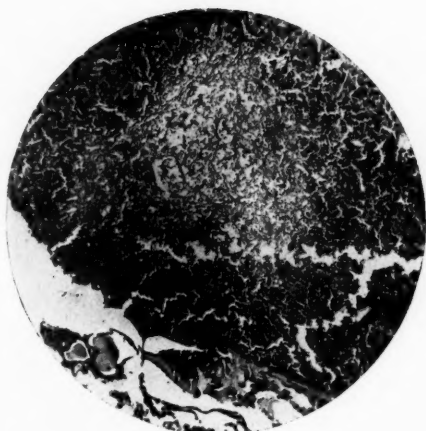


FIG. 4



FIG. 5

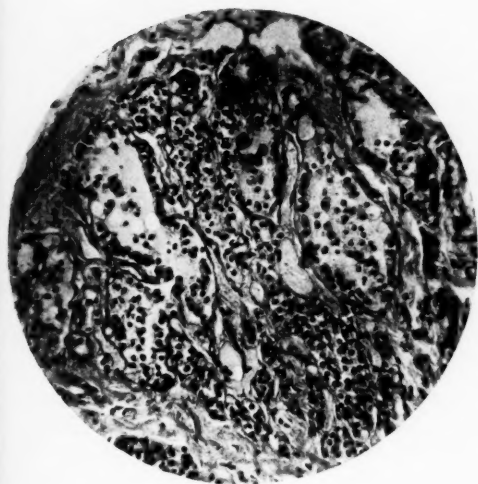


FIG. 6

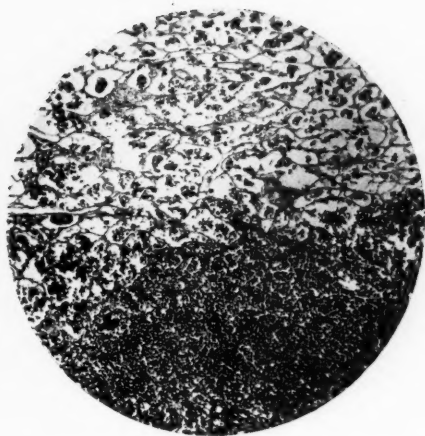


FIG. 7

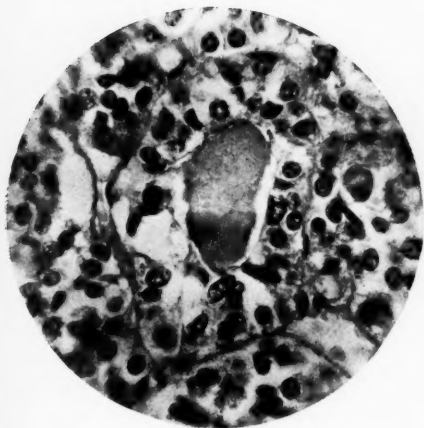


FIG. 8

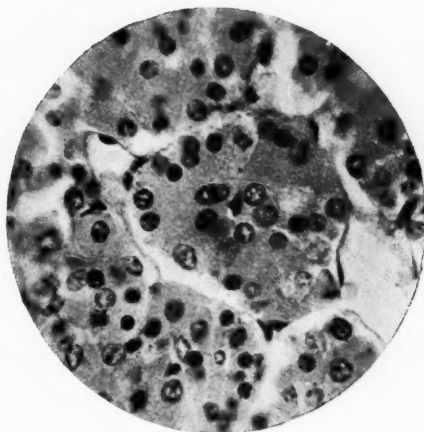
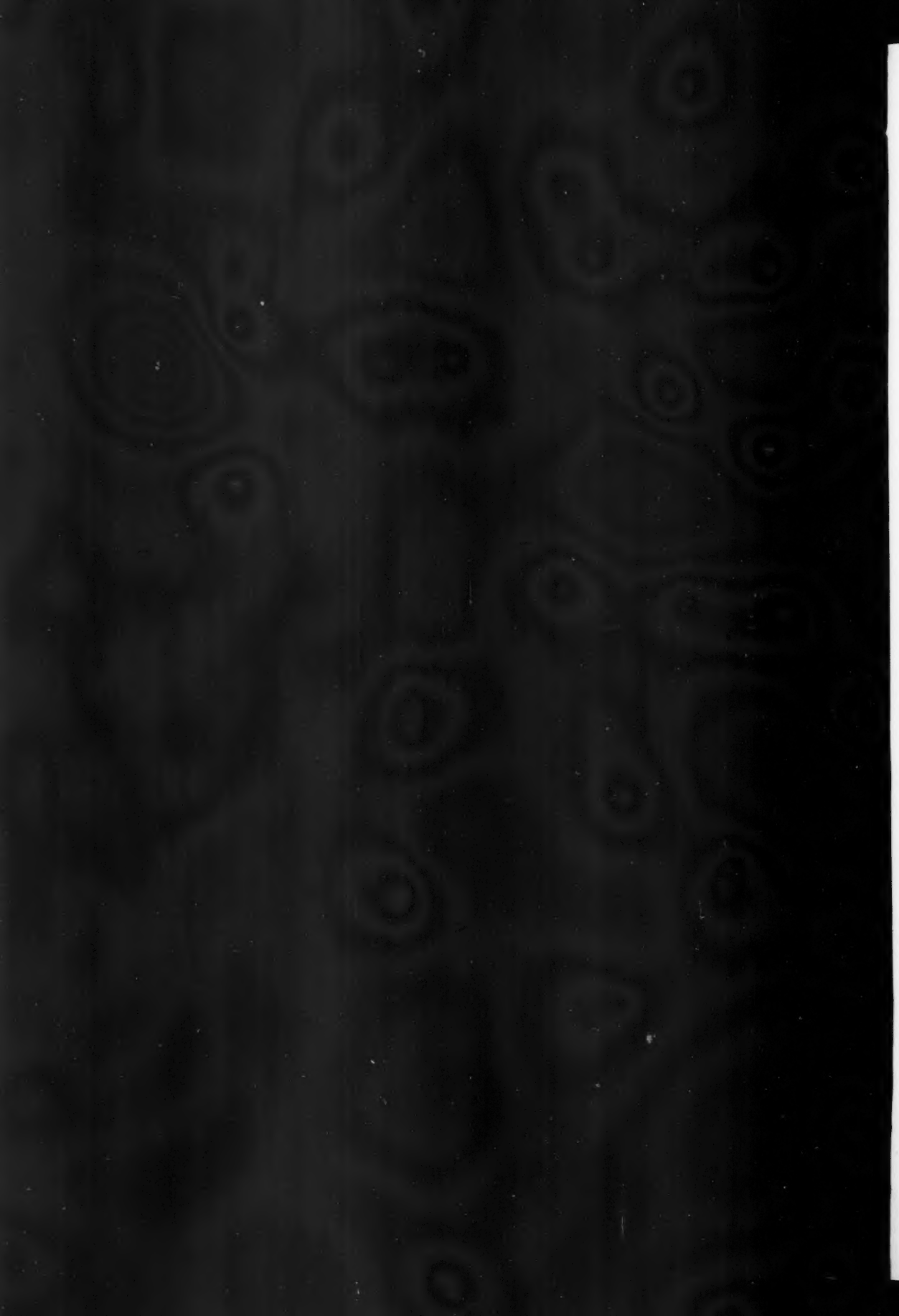


FIG. 9



APPENDIX

DESCRIPTIONS OF SPECIMENS OF PITUITARY GLANDS

I. DIABETES MELLITUS

No. 1. K. S. F. 29. Diabetes mellitus. Coma.

Microscopical report. 1. Pituitary.

Cut surface. Anterior lobe is about equal in size to posterior. Upper border flattened.

Anterior lobe. Towards the anterior border and at the periphery lie the 'chief cells', large, ill-defined, with a finely granular neutrophilic cell body, the protoplasm of which is fairly compact. Nuclei are large, of loose texture, and stain well. Many of these cells show transition into eosinophilic cells, the eosinophilic material surrounding the nuclei. Eosinophilic cells form the bulk of the lobe and are massed together in a compact area towards the centre and posterior end of the anterior lobe. In this region the cells are mainly of the eosinophilic variety, with basophilic cells either isolated or more usually in small clusters. Basophilic cells are numerous at the periphery and throughout the lobe, especially towards the superior and posterior borders.

Into the above compact mass of eosinophilic and basophilic cells extends a mass of colloid from the interglandular cleft. It passes as a narrow wedge almost to the centre of the lobe. In the middle of it are eosinophilic and basophilic cells in all stages of conversion into this colloid. Isolated nuclei are numerous. The colloid is neutrophilic in character and in places finely granular, and interpenetrates the compact cell mass in the centre of the lobe in all directions.

The texture of the lobe is loose towards the anterior margin, but compact posteriorly. Vascular network is rich.

Pars intermedia. The interglandular cleft is widely distended and contains colloid connected with and similar to that above described. Masses of cells amidst the colloid are noticeable. Colloid is in parts basophilic and in parts eosinophilic.

Stalk. In the nervous portion colloid masses with cells in it are noticeable. In the portion of the anterior lobe prolonged upwards on the stalk are very wide cystic spaces lined by flattened or cubical epithelium and containing delicate, finely granular colloid. The cells of this part are of the 'chief cell' type.

Pars posterior. Finely granular masses and colloid are numerous throughout the interstices of the lobe.

2. Pancreas. Head: a small area of fibrosis is present. Glandular tissue presents no gross changes. Tail: a few cystic spaces are seen lined by flattened epithelium, representing distended ducts or possibly degenerated islets of Langerhans.

3. Thyroid. Normal.

No. 2. M. H. F. 32. Diabetes. Coma.

Microscopical report. 1. Pituitary.

Cut surface. Organ was damaged in removal.

Anterior lobe. Cells are mainly chief cells, with neutrophilic, finely granular protoplasm. The outlines of the cells are better defined and the protoplasm is

denser than normal. At the posterior end of the anterior lobe, towards the base of the lobe, is an area of focal necrosis of cells.

Eosinophilic cells are absent.

Basophilic cells are present but are not numerous.

Pars intermedia. Colloid formation at posterior end of anterior lobe and in interglandular cleft is well marked and is much mingled with cells and nuclei, as if active transference of cells into colloid was occurring. Cells in immediate neighbourhood are mainly basophilic. Numerous collections of nuclei are present in this region, with granular degeneration of the protoplasm of the basophilic cells.

Pars nervosa. Golden granules are very numerous in interstices and collections of nuclei.

Very little colloid.

2. *Pancreas.* Tail: islets of Langerhans are extraordinarily numerous and show hyaline degeneration in places. Interacinar fibrosis present. Acinar tissue shows no changes. Head: shows similar changes to those in the tail.

No. 3. B. G. F. 40. Cholelithiasis. Subdiaphragmatic abscess. Diabetes.

Microscopical report. 1. Pituitary.

Cut surface. Upper border flattened. Anterior lobe very large, more than twice the size of posterior lobe.

Anterior lobe. Eosinophilic cells form the lobe, almost to exclusion of all other cells. Nuclei are small, chromatin network well defined, but not dense. Nucleolus present. Cell body is better defined than usual. Protoplasm is compact and stains well with eosin and is very finely granular. Cells tend to be grouped in alveoli or strands, almost adenomatous in character. Eosinophilic colloid formation in places in centre of cells grouped in alveolar arrangement. All stages of transition between the clear 'chief' cells and the granular eosinophilic cells. Chief cells of ordinary characters with faintly staining ill-defined protoplasm situated only at extreme periphery of lobe. Basophilic granular cells scattered throughout lobe and present at periphery, are not numerous.

Pars intermedia. Colloid formation almost absent. Cells mainly eosinophilic. Very little invasion of pars posterior by cells.

Pars posterior. Golden granules very marked throughout lobe.

Colloid formation slight.

2. *Pancreas.* Head: normal. Tail: small area of chronic inflammation present. Acinar tissue normal.

3. *Thyroid.* Normal.

4. *Liver.* Unilobular cirrhosis. Chronic inflammation in portal areas.

No. 4. H. T. 53. Appendix abscess. General peritonitis. Diabetes.

Microscopical report. 1. Pituitary.

Cut surface, semilunar. Upper border concave, lower border convex.

Anterior lobe is formed largely of strands and clumps of neutrophilic granular cells. They are more finely granular and less basophilic than the ordinary basophilic cells and seem to present a stage between the eosinophilic and basophilic cells. In places large masses of aggregated eosinophilic granular protoplasm present, not 'colloidal', with a few nuclei in the mass. This is especially marked towards posterior end, where the cells are crowded together. Cells are well defined and cell bodies frequently vacuolated. Eosinophilic finely granular cells make up the remainder of the lobe, less conspicuous than the more coarsely granular neutrophilic cells. At the periphery and towards the anterior end of lobe the faintly staining ill-defined chief cells are evident. All stages of transition between these cells and the larger neutro-

philic granular cells are very evident. Towards the posterior end of the anterior lobe the neutrophilic cells are larger and grouped in clumps, and here the cells show a definite glandular arrangement. They are grouped around small central spaces containing thin eosinophilic granular colloid. The protoplasm of the cells abutting on the central space is granular, while the outer half is clear and the nucleus is situated at the bases of the cells. The whole strikingly suggests a gland actively secreting (Plate 14, Fig. 2). There is present an increase of the connective tissue and relative diminution of cells, indicating a fibrosis.

Pars intermedia shows some eosinophilic colloid formation. Not present in large amount.

Invasion of pars nervosa by basophilic cells is very noticeable.

Pars posterior. Golden granules in masses throughout the lobe, especially well marked. Wide empty cystic spaces lined by felted neuroglia cells.

2. Pancreas. Head: necrosed. Tail: normal.

No. 5. G. K. M. 14. Diabetes mellitus. Coma.

Microscopical report. 1. Pituitary.

Cut surface. Anterior lobe is not large.

Anterior lobe consists mainly of neutrophilic chief cells. Protoplasm of cell delicate, finely granular, and cell outlines ill-defined. Alveolar arrangement of the cells is noticeable, and in the centre of the alveoli eosinophilic colloid is frequently present in small masses both at the periphery and throughout the lobe. It is present also in the capillaries which are conspicuous throughout the lobe. Texture of the lobe is compact. In the centre of the lobe is a small rounded fibrous area devoid of all cells except a few degenerated ones, but containing blood-vessels. Eosinophilic cells are present in considerable numbers, especially towards the posterior end of the anterior lobe.

Basophilic cells are few in number.

Pars intermedia. Colloid formation is practically absent and the pars nervosa is closely apposed to pars anterior.

Pars nervosa. Shows no colloid masses or golden granules.

2. Pancreas. Acinar tissue normal. Islets of Langerhans few in number.

No. 6. H. K. M. 31. Diabetes mellitus. Coma.

Microscopical report. 1. Pituitary.

Cut surface. Pars anterior slightly larger than pars posterior.

Anterior lobe. Basophilic cells more numerous than eosinophilic, and slightly in excess at the periphery of lobe. Basophilic cells well marked towards posterior end of anterior lobe.

Eosinophilic cells grouped mainly in centre of lobe. Chief cells are not numerous and are present mainly at periphery of lobe. Protoplasm as a whole chiefly basophilic. Texture of lobe loose.

Pars intermedia. Colloid formation is slight. Its place appears to be taken by thin vacuolated protoplasm, resembling that of the chief cells; a few nuclei scattered through it and a few basophil cells. Colloid, where present, is basophil in reaction, with acidophil areas present in it. Present in moderate amount towards posterior end of pars anterior. Collections of nuclei in numbers in region of interglandular cleft. Invasion of pars posterior by basophilic granular cells.

Pars posterior. Very little colloid present in interstices. Golden granules present in fair quantity.

2. Pancreas. Head and tail normal.

3. Thyroid. Normal.

4. Parathyroid. Normal. Slight alveolar arrangement of cells with formation of colloid at one part.

No. 7. P. H. F. 35. Diabetes mellitus. Pregnancy.

Microscopical report. 1. Pituitary.

Cut surface. Anterior and posterior lobes small. Anterior lobe is scarcely larger than posterior. A triangular translucent patch is present at base of anterior lobe, occupying half the lobe.

Anterior lobe. Cellular elements are greatly diminished, and are present only as a thin layer at upper and lower surface of lobe. The middle of the lobe is occupied by a triangular area with its base at the inferior border of the gland and extending from the interglandular cleft behind to the anterior border in front. This area is composed of an irregular meshwork, the original connective-tissue framework of the lobe, the interstices of which contain a finely granular, translucent, colloidal material. Numerous small round nuclei without any apparent cell body are scattered throughout this area. Fibroblasts and connective-tissue cells are also present. Degenerate cells with cell bodies packed with fine golden granules are also noticeable. The capillaries in this area are intact and are filled with red cells.

In the cellular areas the bulk of the cells is made up of rather large cells of the 'pregnancy type'. The protoplasm is well defined, finely granular and neutrophil. In some areas the cell protoplasm is more delicate and is crammed with fine golden granules. A few of the more typical chief cells are evident, but all stages of transition between them and the 'pregnancy' cells are present.

Eosinophilic cells are almost absent.

Basophilic cells are fairly numerous in the cellular areas. A small amount of the eosinophilic colloid is evident among the cells of the anterior lobe, chiefly towards the posterior border of the gland. Definite increase of interstitial tissue is present.

Pars intermedia. The interglandular cleft is empty. There is only a small amount of colloid at the bottom of the cleft.

Pars nervosa. Both golden granules and colloidal bodies are rare except in nervous portion of stalk.

2. Pancreas. Head and tail normal.

3. Thyroid. Proliferation of epithelium lining alveoli with desquamation of cells. Diminution of alveoli and of colloid. Inter-alveolar fibrosis and round-celled infiltration. Great increase of vascular connective tissue (Plate 14, Fig. 6).

No. 8. J. S. M. 43. Diabetes mellitus. Syphilitic meningitis. Suppurating gummata of liver and kidneys.

Microscopical report. 1. Pituitary.

Anterior lobe is about three times the size of the posterior. Upper border convex. A whitish translucent area occupies almost the whole of the anterior lobe except for a rim at its superior and posterior borders.

Anterior lobe is occupied by a large area of necrosis of cells, leaving the delicate connective-tissue meshwork, in the interstices of which lie clumps of granular degenerated cells. Surrounding this area is a band of pus cells, outside which lies a much thickened capsule of layers of fibrous tissue, with fibroblasts and connective-tissue cells. At the region at the base of the stalk and along the posterior border of the anterior lobe can be seen more or less degenerate masses of the ordinary cells of the anterior lobe, mainly basophilic with a few eosinophilic cells. These are mingled with polymorphonuclear and lymphoid cells, with connective-tissue cells and fibroblasts. The connective-tissue trabeculae are thickened and oedematous. Clumps of long Gram-negative bacilli can be seen in the necrosed area. Chief cells are very few in number. Scarcely any normal cellular tissue is present in the anterior lobe (Plate 14, Fig. 7).

Pars intermedia. Interglandular cleft is absent and there is no colloid present.

The posterior lobe abuts directly upon the anterior lobe.

Posterior lobe presents a normal appearance except for a slight invasion by polymorphonuclear cells close to its anterior border at its junction with the anterior lobe. The cells and fibres are not degenerated. Clumps of golden granules are present in considerable quantities. A few eosinophilic granular masses of colloid with eosinophilic finely granular debris are present in the interstices.

Stalk. The cells lining the anterior and posterior surface of the stalk are swollen and the connective-tissue trabeculae infiltrated and oedematous. The lumen of some of the capillaries contain fine thrombi. Some colloid masses are present in the capillaries. The nervous portion contains some eosinophilic granular debris. No colloid masses present.

2. **Pancreas.** Head and tail: large areas of fibrous tissue, especially around the ducts. Acinar tissue normal.

3. **Thyroid.** Normal.

4. **Liver.** Syphiloma. Liver cells in various stages of degeneration within large areas of inflammatory tissue encapsulated by fibrous tissue. Polymorphonuclear and plasma cell infiltration with marked fibrosis.

4. **Kidney.** Syphiloma. Chronic inflammation with large areas of acute suppurative inflammation.

II. ACUTE PANCREATITIS.

No. 1. W. R. M. 33. Acute pancreatitis.

Microscopical report. 1. Pituitary.

Cut surface. Anterior lobe is large, more than double the size of the posterior lobe.

Anterior lobe is composed chiefly of eosinophilic cells, crowded together in masses, especially towards the centre and posterior end of anterior lobe. The cells are large and generally discrete, with a finely granular protoplasm and a small pyknotic nucleus. Basophilic cells are less numerous, generally grouped in masses both at the periphery, and at intervals in the centre of the lobe. The chief cells are comparatively few in number and are situated chiefly at the periphery. The cells are rather larger than is usually the case, and the protoplasm is finely granular and more dense and the cell outlines better defined. The vascular channels are very evident.

Pars intermedia. No colloid formation present.

Pars posterior. Golden granules in masses of varying size are present throughout the lobe. Towards the region of the pars intermedia finely granulated eosinophilic colloid masses of considerable size are situated.

2. **Pancreas.** Acute haemorrhagic pancreatitis. Thrombosis of vessels.

3. **Liver.** Well-marked fatty degeneration of the cells with chronic interstitial inflammation.

No. 2. L. B. M. 50. Acute pancreatitis.

Microscopical report. 1. Pituitary.

Cut surface. Anterior and posterior lobe are about equal in size.

Anterior lobe is composed mainly of chief cells in clumps.

Basophilic cells in strands or groups are present in moderate numbers throughout the lobe, and about equal in number the eosinophilic cells.

Eosinophilic cells are not numerous and are chiefly grouped towards the posterior end of the anterior lobe.

Colloidal masses are somewhat numerous, small in size, and usually in the

centre of a group of cells disposed in an alveolar manner. Colloidal masses contain nuclei here and there. Colloid is chiefly eosinophilic. Interstitial tissue forms a loose network.

Pars intermedia. Colloid is present in big masses, in centre of large alveoli lined by flattened cells. A little colloid at posterior end of anterior lobe, mingled with nuclei and discrete eosinophilic cells. Some basophilic cells at base of pars intermedia and basophilic colloid present.

Pars posterior. Colloid masses are few but of large size. Golden granules are few.

2. Pancreas. Acute pancreatitis with areas of fat necrosis.

No. 3. A. T. F. 78. Acute pancreatitis.

Microscopical report. 1. Pituitary.

Cut surface. Anterior lobe is but little larger than posterior. Stalk is attached to anterior lobe midway between its anterior and posterior borders.

Anterior lobe. Cells are mainly of the normal chief cell type, small, with indefinite outline and very little delicate, finely granular protoplasm. Nuclei are small and compact.

Eosinophilic cells are present in the centre of the lobe but are not numerous.

Basophilic cells are infrequent.

Colloid formation is a noticeable feature. The colloid masses are small, eosinophilic, and many contain golden highly refractile granules. The cells are arranged in an alveolar manner around them. They lie mainly in the centre of the lobe.

Texture of the lobe is very loose; the delicate connective-tissue structure is very evident. Capillary network is engorged as well as vessels in capsule.

Pars intermedia. Colloid formation is slight, but contains the same highly refractile golden granules as in colloid of anterior lobe.

Pars posterior. Masses of golden granules, similar to that in the colloid, are very noticeable throughout the lobe. Colloid formation is also present in the interstices in moderate amount.

Stalk is richly vascular.

2. Pancreas. Acute pancreatitis. Fat necrosis.

3. Liver. Acute cholangitis present.

III. CARCINOMA OF PANCREAS.

T. L. M. 56. Carcinoma. General metastases.

Microscopical report. 1. Pituitary.

Cut surface. Anterior lobe scarcely larger than posterior. Upper border concave.

Anterior lobe. Cells are comparatively few in amount and are mainly eosinophilic cells in groups and situated towards the anterior half of lobe. Cells are large, of well-defined outline. The remainder of the lobe is composed of strands of chief cells, with very little protoplasm, so that they appear almost as masses of nuclei. The nuclei are compact and stain well, and are especially situated towards posterior end of anterior lobe. Interstitial tissue is increased in amount, forming fibrous trabeculae. Vascular channels are wide and for the most part empty, so that texture of lobe appears loose.

Pars intermedia. Interglandular cleft is empty and colloid formation is almost absent.

Pars posterior. Texture of lobe is loose and open. Colloid masses in

interstices are very few. Golden granular masses are present in great amount throughout lobe.

2. Pancreas. Columnar-celled carcinoma.

3. Liver. Columnar-celled carcinoma.

IV. MYXOEDEMA.

No. 1. F. W. F. 47.

Microscopical report. 1. Pituitary.

Cut surface. Anterior lobe double the size of posterior. Pars intermedia well marked.

Anterior lobe is composed of cells with indefinite boundaries resembling chief cells. Large plasmodial masses are present. The cells are, however, larger than chief cells, often discrete, cubical and columnar in shape, large, with a faintly staining, finely granular basophilic protoplasm. Nucleus is large, poorly staining, with a loose chromatin network and well-marked nucleoli. The cells are arranged in many instances to form alveoli containing eosinophilic colloid. The cells are numerous and compact. Colloid is present, either in the alveoli or in the supporting stroma, in marked amount, and is both basophilic and eosinophilic.

Basophilic cells are numerous, grouped in strands or alveoli, both at the periphery and in the centre of the lobe.

Eosinophilic cells almost absent.

Fibrosis of interstitial stroma.

Pars intermedia. Colloid formation is very marked in large dilated alveoli. Largely basophilic in character; some colloid eosinophilic or basophilic with eosinophilic masses in it. Colloid evident in small alveoli of pars intermedia on anterior aspect of stalk.

No invasion of pars posterior by cells.

Pars posterior. Very little colloid. Golden granules are numerous, with marked granularity of nervous tissue.

Stalk shows no colloid. Granularity of nervous portion marked.

2. Thyroid. Extreme fibrosis. Marked round-celled infiltration, especially in region of alveoli. Alveoli diminished both in number and size. Many alveoli are empty and colloid is diminished. Proliferation and desquamation of cells into lumen of alveoli amid colloid.

Strands of cells resembling parathyroid tissue.

3. Pancreas. Head: normal. Tail: granular degeneration and vacuolization of cells of islets of Langerhans. Slight interacinar fibrosis with degeneration of some of the acinar cells.

4. Adrenals. Vacuolization of cells of cortex. Slight fibrosis. Medullary and chromaffin tissue well marked.

5. Ovaries. Extreme fibrosis. Sclerosis of corpora lutea. Cysts present. No germinal follicles remain.

6. Skin. Marked thickening of corium with fibrosis and oedema. Thickening of vessels. Atrophy of glandular structures. Proliferation of corneal strata.

No. 2. K. W. F. 46. Myxoedema. Empyema.

Microscopical report. 1. Pituitary.

Cut surface. Anterior lobe is much hypertrophied, broad and flattened. Pars posterior is small and compressed.

Anterior lobe is composed of cells of the 'chief cell' type, closely compressed together in great masses and strands. The cells are of very indefinite outline,

with a moderate amount of cytoplasm, which is finely granular and usually neutrophilic. Nuclei are large with well-defined network. All stages of transition are noticeable between these cells and the eosinophilic and basophilic cells, of which the basophilic are more numerous than the eosinophilic, though eosinophilic cells are present in moderate amount scattered amid the other cells.

Basophilic cells are large and well defined. Their cytoplasm occasionally presents large vacuoles, and they are grouped chiefly towards the periphery in clumps or strands. Eosinophilic cells are infrequent, mainly situated in centre of lobe.

Masses of colloid are present mingled with red cells in the blood-vessels and in the interstitial spaces. Masses of granular material, apparently degenerated cells, are very evident. The capillary network is rich, but there is a marked increase of fibrous tissue.

Pars intermedia. Large alveolar spaces filled with colloid are fairly numerous, lined by flattened or cubical cells. Ducts pass back from them into the *pars nervosa*. They are lined by cubical cells and open in front into the alveoli. The colloid extends among the meshwork of cells at the posterior end of the anterior lobe, so that discrete cells lie among the colloid. Colloid masses extend forward along the upper surface of the anterior lobe beneath the capsule. Colloid is thin and in places vacuolated and contains numerous nuclei. Basophilic cells are predominant in this region and the colloid varies in reaction from eosinophil to basophil.

Pars nervosa. The cellular elements are compact and granular. Colloid masses in the interstices are fairly numerous. Golden granules are numerous throughout the lobe.

2. Thyroid. Thyroid tissue not found.

3. Adrenals. There is a marked increase in the thickness of the cortex with adenomatous formations and vacuolization of the cells. Capsule thickened.

Medulla appears to be diminished by fibrosis. Some round-celled infiltration which is not abnormal. Chromaffin tissue appears to be reduced in amount.

4. Pancreas. Normal.

5. Ovaries. Marked fibrosis with sclerosis of corpora lutea. No ovarian epithelium remains.

V. GOITRE.

M. F. F. 18. Goitre.

Microscopical report. 1. Pituitary.

Cut surface. Anterior lobe about equal to posterior in size.

Anterior lobe. Eosinophilic cells very numerous, forming the bulk of anterior lobe, grouped mainly towards the centre and posterior part of gland. Cells are crowded together in large masses and the interstitial network is diminished. Basophilic cells are fairly numerous and present mainly at the periphery. Chief cells are little in evidence and chiefly present at periphery.

Pars intermedia. Colloid present in considerable amount, in alveoli lined by sub-columnar epithelium. Cells of *pars intermedia* resemble chief cells and are grouped in well-defined alveoli. No invasion of *pars posterior* by cells.

Pars posterior. Considerable amount of colloid in the interstices throughout lobe. Golden granules are few. Meshwork of lobe is very compact. Pale round granular bodies are very numerous throughout the lobe, especially at the base of the stalk.

Stalk. The same granular masses are very evident in the nervous portion of the stalk in large numbers.

2. Thyroid. Great increase of colloid with marked distension of alveoli, forming a cystic adenoma.

3. Parathyroid. Normal. Well-marked alveolar formation enclosing colloid at one part.
4. Thymus. Large numbers of Hassal's corpuscles in all stages of degeneration, some calcified. Lymphoid cell tissue normal.
5. Adrenals. Normal.
6. Pancreas. Head and tail normal.
7. Ovaries. Right: large masses of lutein cells distributed throughout the tissues. Large cystic spaces containing granular colloid in which lie convoluted strands of cubical epithelial cells. Left: normal. Small colloid cyst present.
8. Spleen. Marked congestion. Diminution of Malpighian corpuscles.

VI. ADDISON'S DISEASE.

W. McG. M. 18.

Microscopical report. 1. Pituitary.

Cut surface. Posterior lobe is small compared with the anterior.

Anterior lobe is composed of rather closely packed masses of neutrophilic 'chief cells' displaying their usual characteristics. Basophilic cells, large and with well-defined outlines, are numerous throughout the lobe, more especially towards the centre than at the periphery. Eosinophilic cells are present in rather fewer numbers, and grouped chiefly towards the posterior end of anterior lobe. Transitional stages between them and the 'chief cells' are noticeable. Colloid is absent and the connective-tissue meshwork and capillaries inconspicuous.

Pars intermedia. Alveolar spaces are present but colloid is absent.

Pars nervosa. Basophilic cells and duct-like alveoli lined by columnar cells are especially noticeable towards the anterior margin in the region of the interglandular cleft. Colloid is not noticeable, but fine granular debris is everywhere present in the interstices of the lobe and in the nervous portion of the stalk.

2. Adrenals. Right and left: no normal adrenal tissue seen. Calcified tuberculous tissue.

3. Pancreas. Normal.

4. Thyroid. Normal.

5. Buccal mucosa. Marked pigmentation in deepest layers of mucosa. None in corium.

VII. STATUS THYMO-LYMPHATICUS.

W. W. M. 4 months.

Microscopical report. 1. Pituitary.

Cut surface. Anterior and posterior lobes are about equal in size.

Anterior lobe is composed mainly of neutrophilic chief cells.

Eosinophilic cells are numerous throughout the lobe.

Basophilic cells are present also, but rather less numerous than the eosinophilic cells.

Pars intermedia shows no colloid.

Pars nervosa shows no colloid or granules.

2. Thymus. Normal in appearance, apart from marked hyperplasia.

3. Testicle. Right: fibrosis. Atrophy of glandular tissue. Marked chronic inflammation. Left: normal. Glandular tissue not yet differentiated.

ACHALASIA OF THE CARDIA

BY ARTHUR F. HERTZ

With Plates 15 and 16

I. *Achalasia of the Cardia (so-called Idiopathic Dilatation of the Oesophagus or Cardiospasm).*

Definition and History. Dilatation of the oesophagus without organic obstruction was first described by Hannay (1), who published a detailed clinical history and pathological report of a case in 1833. In 1882 Mikulicz (2) suggested that it was due to spasm of the cardia, and in recent years the term 'cardiospasm' has almost entirely replaced the earlier designation of 'idiopathic dilatation of the oesophagus'. It is probable, however, that the former name is equally incorrect, and that the dilatation and hypertrophy of the oesophagus are due to achalasia or absence of the normal relaxation of the cardia. For the word 'achalasia' I am indebted to Sir Cooper Perry, who coined it for me, as it was obvious that the word 'cardiospasm' and the erroneous idea it conveys would never be discarded unless some less cumbersome expression than 'absence of relaxation' was devised.

Pathology. Zenker and Ziemssen (3) in 1877 and Morell Mackenzie (4) in 1884 believed that the condition was due to 'diminished contractile power' or 'general weakness' of the muscular coat of the oesophagus. This theory did not, however, explain the hypertrophy, which is always present and which indicates that the oesophagus must have made violent efforts to overcome some obstruction; it is to the failure of these efforts that the dilatation must be due. As no organic obstruction is ever found, the cardiac orifice after death being of normal size and admitting the passage of a finger without any difficulty, it is clear that the obstruction must be functional. Since the suggestion was first made by Mikulicz that the functional obstruction is due to a spasm of the cardiac sphincter, nearly all writers have adopted this view, and the condition is now generally known as cardiospasm. As the symptoms may be present without intermission for many years before death, it is obvious that a considerable degree of hypertrophy of the cardiac sphincter would result from the long-continued spasm. The rapidity with which hypertrophy develops in a spasmodically contracted sphincter is well seen in hypertrophic pyloric stenosis of infants, and it is inconceivable that a spasm of the cardia could last as many years as the spasm of the pylorus lasts weeks without giving rise to hypertrophy. In none of the specimens I have seen, however, and in none of recorded autopsies has there been any hypertrophy of the cardia, the normal state of which has been in striking contrast with the hypertrophy of the oesophagus itself. Considerations of this sort led Rolleston (5) in 1895 to

suggest that the dilatation of the oesophagus might be due to 'a failure in the co-ordinating mechanism by which the cardiac sphincter is relaxed during swallowing', and he suggested that 'paralysis or continued inhibition of the longitudinal muscular fibres of the oesophagus would allow dilatation of the tube to occur, and at the same time by interfering with the opening of the cardiac sphincter would induce hypertrophy of the circular muscular coat'.

Without knowing of Rolleston's view, I came to a somewhat similar conclusion about five years ago. On watching the process of swallowing with the X-rays, the barium-containing food is seen to pass very quickly down the oesophagus to the cardia, where there is a momentary pause, the lower extremity of the shadow ending as a fine point corresponding to the cardiac orifice of the stomach (Fig. 1). A moment afterwards the food is seen to pass on

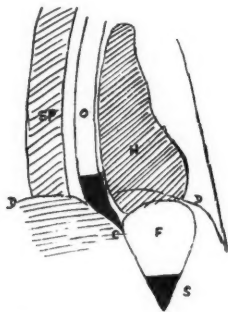


FIG. 1. X-ray appearance of oesophagus in right antero-lateral position when a mouthful reaches the cardia; an earlier mouthful has already entered the stomach.

O, oesophagus; C, cardia; F, fundus; S, barium-containing food already in stomach; SP, spine; H, heart; D, D, diaphragm.

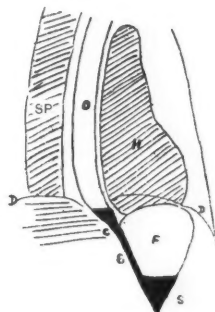


FIG. 2. X-ray appearance immediately after Fig. 1, the cardia having relaxed, so that a stream of barium-containing food, B, runs down the inner wall of the fundus through the relaxed cardia, C, to join the food already in the stomach, S.

into the stomach, and where the shadow ended before as a fine point a shadow almost as wide as the oesophagus itself is now seen (Fig. 2). The obvious explanation is that when a peristaltic wave has carried the food to the closed cardia, the latter widens owing to active relaxation of the circular muscle-fibres, which surround it and form the cardiac sphincter. It has been stated that there is no definite thickening of the muscle at this point corresponding to the sphincters at the pyloric and ileo-caecal orifices, but Professor Keith has demonstrated to me that this is incorrect and that a true cardiac sphincter does in fact exist. My X-ray observations are confirmed by experiments on animals, which show that the cardia relaxes when each peristaltic wave, passing down the oesophagus in the act of swallowing, reaches its lowermost end, just as the pyloric sphincter relaxes when each gastric peristaltic wave reaches it. Cannon (6) has shown that section of the vagi in animals below the origin of the recurrent laryngeal nerves prevents the normal relaxation and leads to the accumulation of food in the oesophagus, which consequently becomes dilated. I believe that under certain conditions a similar phenomenon occurs in man: there is an absence of

relaxation—achalasia (α , not; χαλᾶω, relax)—so that the oesophagus continues to end as a sharp point (Plate 15, Fig. 3). Consequently food stagnates in the oesophagus, which dilates as more and more collects in it; the distension of the oesophagus acts as a powerful stimulus to peristalsis, which is not only excessively violent, as is easily seen with the X-rays, but continues more or less all day without intermission, instead of occurring only in single waves as each mouthful is swallowed. This is the cause of the hypertrophy.

In correspondence with this view I have found that in spite of the fact that strong peristaltic waves are unable to overcome the obstruction, the weight of an india-rubber tube filled with mercury is sufficient to cause it to drop without the slightest difficulty through the cardia into the stomach, the actual passage through the cardia being often inappreciable to the hand which holds the mercury bougie. With the aid of the X-rays I have several times watched it pass directly into the stomach, as if it met with no resistance at all. This would be quite impossible if the obstruction was due to spasm: the resistance offered to the introduction of the finger, for example, when the anal sphincter is in a condition of spasm is very considerable, and considerable force is required to overcome it. Moreover, the tube can be withdrawn with equal ease: it is not gripped, as it would be were a spasm present, and as the finger is gripped when it is withdrawn from a spasmodically contracted anal sphincter. I have seen one case of combined achalasia and cardiospasm, an officer 33 years old, who had had all the symptoms of achalasia for three years, but the mercury tube met with some obstruction when introduced and was tightly gripped when withdrawn. This only occurred on the first two occasions, the contrast afterwards when the cardiospasm had disappeared being very striking; the achalasia was also rapidly cured. Mathieu and Roux (7) describe a case of hysterical spasm of the oesophagus, in which it was impossible to withdraw an oesophageal sound until the patient was deeply anaesthetized with chloroform.

In the majority of cases of achalasia of the cardia no obvious cause can be discovered either during life or after death. In a few, however, an ulcer or carcinoma of the stomach has been present, the achalasia being then due to reflex inhibition of relaxation, just as achalasia of the ileo-caecal sphincter may be a reflex result of appendicitis. In others inflammation or ulceration of the lower end of the oesophagus has been found with the oesophagoscope or at the autopsy; this is doubtless often due to irritation by the decomposition products of food retained in the dilated oesophagus, but it may sometimes be primary, the achalasia of the cardia being then due to a reflex inhibition, comparable to achalasia of the pyloric sphincter (so-called pylorospasm) due to gastric ulcer, achalasia of the ileo-caecal sphincter due to Lane's kink, and achalasia of the anal sphincter due to chronic appendicitis, but an ulcer in the immediate neighbourhood of the cardia would probably give rise to a true spasm, just as an ulcer involving the pyloric and anal canals gives rise respectively to pylorospasm and anal spasm. One of my patients had mitral stenosis and a very dilated left auricle; the latter was probably the source

of the reflex inhibition of relaxation. In rare cases achalasia may be due to a lesion of the vagus, degeneration of which was discovered in one case by Krause; this may also have been the cause in a boy, in whom achalasia developed after whooping-cough (Rolleston (5)).

The lower two-thirds of the oesophagus are generally most dilated. The dilated oesophagus may be able to hold as much as a pint, and its circumference may exceed six inches, but owing to the resistance offered by the border of the oesophageal aperture in the diaphragm, there is comparatively little dilatation here and in the intra-abdominal portion of the oesophagus. The oesophagus may be lengthened as well as dilated; it then runs a somewhat tortuous course through the thorax.

Achalasia of the cardia may begin at any age: the age at onset in six of my own patients was 26, 30, 36, 40, 48 and 65, and cases have been recorded which began at 8 and at 70. Five of my patients were males and two females, but among all the published cases the sexes are equally affected.

Symptoms. The condition generally develops gradually, a slight attack lasting for a day or two being followed by a period of freedom for a few days or even several weeks or months; other attacks then occur at gradually shorter intervals, until finally the condition becomes permanent. In the intervals between the early attacks the patient feels perfectly well, and I have been unable with the X-rays to detect anything abnormal in the act of deglutition. The attacks often begin in the morning, and the patient realizes he is going to have one from the difficulty he experiences in swallowing saliva when he wakes. He feels as if the food 'sticks'; he often recognizes that the obstruction is beneath the lower end of the sternum, but sometimes the sensation is felt in the upper part or middle of the chest. The patient realizes that food 'won't go down'; it feels as if 'the passage is closed', and the food 'fills up' or 'blows out' the chest. Sometimes actual pain is produced, and in one case a slighter pain was felt at the same level behind. The patient may notice gurgling in the chest, as if 'gas was bubbling through water'. Salivation occurs in almost every case; the saliva is frothy and contains much mucus, and large quantities may be rejected; thus one patient of mine spat out ten ounces during a single night.

As a rule the patient voluntarily relieves his discomfort within a few minutes of finishing a meal by bringing up the greater part of what he has eaten, mixed with saliva. He can generally do this quite easily, but occasionally requires to produce a vomiting reflex by tickling his throat; in neither case is there any nausea. It is uncommon for the food to be returned quite involuntarily, but this may happen if a large quantity has been retained in a greatly dilated oesophagus sufficiently long for a certain amount of bacterial decomposition to occur, when the products may irritate the oesophagus and cause its contents to be rejected. One patient of mine always felt more comfortable after drinking cold water; he recognized that it did not reach his stomach, as he had a full and cold sensation which extended from below upwards, until he finally brought the water up by a voluntary effort.

Most patients can swallow fluids more easily than solids, but one of my patients could retain solids more easily and always avoided drinking fluids with her meals. The food is retained most easily if it is swallowed extremely slowly.

The weight of the column of food in the dilated oesophagus after a meal is sufficient to force a small proportion of the fluid present through the cardia as a very narrow stream, but as soon as the weight of the column falls below a certain point or the individual lies down, the pressure becomes insufficient and the flow ceases. Consequently food stagnates in the oesophagus for an indefinite period, and a considerable quantity can be removed from it even after a fast of twenty-four hours.

The oesophagoscope shows that the cardiac orifice is completely closed. The mucous membrane, especially in the lowest part of the oesophagus, may be normal, but it is often red and inflamed, and there may be superficial erosions, which are probably in most cases secondary to the stasis.

The general health at first remains perfectly good in contrast to what occurs in malignant obstruction of the oesophagus and in spite of the fact that weight is rapidly lost; thus one patient lost two stone in the three months following the onset, but felt otherwise as well as ever. After a certain amount of weight is lost, a condition of equilibrium appears to develop; though only extremely small quantities of food reach the stomach, the patient loses no more weight, and though he is less strong than formerly, he may continue to live in this condition for many years and reach old age. Owing to the small quantity of food residue reaching the colon, the patient is naturally very constipated.

Diagnosis. The patient's description of his symptoms is generally so characteristic that a diagnosis of oesophageal obstruction can be made with a considerable degree of probability. This is confirmed most easily and with greatest certainty by means of an X-ray examination, the patient eating thick porridge mixed with milk and barium sulphate: the use of capsules containing opaque salts is much less satisfactory, as I have seen them stick in the oesophagus of normal individuals for several minutes. It is most important that the examination should be made during an attack: one of my patients had previously been twice examined with the X-rays and had been told that nothing was the matter, as no obstruction was found owing to the examination having been made in the intervals. The possibility of achalasia should always be considered if the obstruction is found to be situated at the cardia.

When obstruction at the cardiac orifice has been diagnosed it is next necessary to ascertain whether this is due to achalasia or to organic disease: the only organic disease which requires consideration is cancer, as non-malignant strictures are extremely rare, except as a result of caustic poisoning, when a history is generally obtainable and the stricture is found to extend for some inches upwards from the cardia instead of being strictly confined to the cardia. The intermittent character of the early attacks, the absence of all constitutional

symptoms in spite of rapid loss of weight, the comparatively early age at onset with many patients, and, in cases in which an early diagnosis is not made, the long duration of the illness point to achalasia rather than growth. The contrast between the perfectly normal oesophagus seen with the X-rays when an examination is made in the intervals between the attacks in the early stage and that seen during an attack is characteristic of achalasia, as very little variation is observed at different times in cancer. The even outline of the shadow and the localization of the obstruction to the cardia in achalasia differ from the more irregular outline and the more extensive area of obstruction in cancer, but neither of these points is conclusive, as in very early cancer of the cardia the X-ray appearance may be indistinguishable from that of achalasia. The only conclusive evidence is the great ease with which a mercury tube passes through the cardia in achalasia in contrast to the complete obstruction offered to its passage by a growth. An ordinary bougie is less satisfactory, as it may impinge against the dilated lower end of the oesophagus immediately above the diaphragm, and it is therefore often difficult and sometimes impossible to pass one in achalasia. In cases of many years' standing the saccular lower end of the oesophagus may be so large that it reaches below the cardiac orifice: in one such case the mercury bougie was only passed after several unsuccessful attempts had been made, but the long history excluded a growth.

Prognosis. If the condition is recognized at the onset of symptoms, a permanent cure often results from treatment, but if treatment is only instituted when the condition has become continuous and the oesophagus greatly dilated, cure as distinct from mere relief of symptoms is less likely to be obtained; thus Myer and Carman (8) have shown that patients treated by Plummer's method have to eat slowly and chew thoroughly in order to avoid a return of symptoms, as the dilatation of the oesophagus persists. In very acute cases death has occurred at an early stage, but more often the patient survives for a considerable period, even for twenty or more years, although only a minute quantity of food ever reaches his stomach.

Treatment. The simplest and most effective treatment is by means of a mercury tube. The tube has a rounded end with no holes in it, its diameter being 24 gauge; it is advisable, however, in the first examination to pass a tube of 20 gauge before using the larger one. It is filled with mercury, the upper end being closed. A string is attached to the upper end to prevent the possibility of its dropping into the stomach, and two circles are marked on the bougie at distances of sixteen and seventeen inches respectively from its lower extremity. The tube drops through the cardia; it requires no pushing and can be easily managed by the patient himself. It is kept in position for a few minutes on each occasion at first, but later it can be withdrawn directly after it has entered the stomach. The lower extremity should not pass more than an inch beyond the cardia, which is situated on an average sixteen inches from the teeth, as otherwise indigestion may result from irritation of the stomach. The patient feels relieved and realizes that 'the passage is clear' as soon as it is withdrawn.

It should be passed immediately before meals: the food then enters the stomach without difficulty. In very early cases the tube may only need to be passed once: in my first case an ordinary bougie was passed the day after the symptoms commenced, and it was never necessary to pass it again. Generally, however, the tube has to be passed before each meal at first: then it can be passed once a day and gradually less often, till finally it is only passed at rare intervals, when the patient feels that some slight obstruction is returning.

In very rare cases, when the oesophagus has become greatly dilated and the lower end forms a pouch which extends below the cardia, the end of the tube generally misses the cardia and curls round in the pouch. A trial should then be made of the method of treatment devised by Russell in 1898 and more recently improved by Plummer (9), which has been rendered superfluous in most cases by the introduction of the mercury tube. The patient slowly swallows three yards of silk thread in the afternoon and another three yards the following morning; sufficient reaches the intestine to prevent its withdrawal when it is pulled tight. A tube is threaded over the silk through the cardia, which is then forcibly dilated by the inflation of a bag attached to the tube.

II. *Waterbrash.*

The condition called waterbrash, the *vomissement pituiteux* of French authors, and certain associated phenomena can be most satisfactorily explained as due to a special form of achalasia of the cardia.

At a certain interval after a meal, which varies in different cases, but is fairly constant for each individual, an uncomfortable sensation of constriction, which may amount to severe pain, is felt deeply beneath the lower end of the sternum. This may be accompanied by profuse salivation, which was so great in one of my cases that pain was felt in the jaws, doubtless owing to the capsule of the parotid glands being stretched by the hyperaemia of the unusually active glands. Occasionally the substernal discomfort or pain disappears spontaneously after a more or less long interval, but more frequently relief only occurs on vomiting a few mouthfuls of clear fluid, which is generally described by the patient as being like water (waterbrash), though it sometimes contains a good deal of mucus. The fluid is never sour in uncomplicated cases, but it may taste slightly salty or sweet. The vomiting is rarely accompanied by much straining, and the fluid may even rise into the mouth without any effort at all; it is rarely preceded by nausea. It is sometimes repeated two or three times at intervals of ten to twenty minutes.

It is clear that the fluid must come from the oesophagus and not from the stomach, as even when the previous meal was large and has only been finished within an hour, no food is present in the regurgitated material, which is alkaline in reaction and has all the characters of pure saliva, although it is quite obvious that the stomach must still contain a considerable quantity of food mixed with gastric juice. That this is the case is sometimes proved when a few mouthfuls

of gastric contents, recognized by their acid taste and reaction and by the presence of partially digested food, are vomited as a result of straining immediately after the clear food has been brought up. Moreover, the volume of saliva vomited each time is generally between 60 and 120 c.c., which appears to represent the amount of fluid which the undilated oesophagus can retain without rejecting.

The vomiting is sometimes preceded by an obviously excessive flow of saliva, but more frequently no abnormal salivation is recognized by the patient, the saliva accumulating in the oesophagus without the patient being aware of its presence. The accumulation of fluid in the oesophagus is clearly the cause of the discomfort or pain felt beneath the end of the sternum.

Waterbrash may persist for years without any other evidence of indigestion, but it is generally associated with some form of functional or organic gastric disease, and I have seen well-marked waterbrash in several patients with duodenal ulcer. It occurs particularly in conditions associated with gastric hypersecretion, probably because they also give rise to reflex hypersecretion of saliva, but Mathieu has observed it at the onset of gastric carcinoma.

The oesophageal origin of the fluid was first suggested by Mathieu (10), but he thought that the accumulation was due to cardiospasm, which was due to a reflex from the stomach produced by its irritating contents or by some lesion which also caused excessive salivation.

It seems to me more likely that when the flow of saliva is moderately excessive, it runs down the oesophagus without the patient's knowledge and without the aid of actual swallowing: the cardia is naturally closed and the fluid therefore collects above it in the lower end of the oesophagus. Cannon (11) has shown that the presence of free hydrochloric acid in the stomach tends to inhibit the relaxation of the cardia. Hence gastric hypersecretion, which is the chief cause of excessive flow of saliva, tends at the same time to prevent the relaxation of the cardia. The food does not accumulate in the oesophagus, as the cardia relaxes during swallowing: thus I have never seen any stasis of the food in the oesophagus on examining a case with the X-rays. When obvious salivation occurs and the patient makes repeated deglutition acts the cardia might be expected to relax; but by this time an excessive quantity of hydrochloric acid has accumulated in the stomach and inhibits the relaxation of the cardia, even when the swallowing acts cause peristaltic waves to reach the lower extremity of the oesophagus.

It is possible that the morning vomiting of alcoholic individuals is due to a similar process, although it is accompanied by more violent vomiting efforts. In this case the fluid consists of saliva mixed with a considerable proportion of pharyngeal and oesophageal secretion, as catarrhal pharyngitis and oesophagitis are frequently associated with the catarrhal gastritis of alcoholic patients. As there is no gastric hypersecretion in alcoholic gastritis, reflex inhibition of relaxation would not occur, the accumulation being due to excess of fluid running down the oesophagus during the night without the aid of actual

deglutition. When the vomiting is violent the stomach may empty itself later, the fluid then brought up being bile-stained and sometimes faintly acid in reaction.

In some cases slight regurgitation of the gastric contents into the oesophagus may occur before the accumulation of saliva is ejected, so that the vomited material contains a small proportion of the gastric contents.

A variety of waterbrash, which appears to be very much more common in France (12) than in England, where it is almost unknown, occurs in hysterical individuals, who vomit a few mouthfuls of alkaline watery fluid, which is red as a result of the admixture of the saliva with blood, the origin of which is unknown; possibly it comes from the gums, as hysterical patients may simulate haemoptysis by spitting blood which they have sucked from this source. Occasionally a trace of gastric contents may be present and cause the blood to be brown; the darkening increases after the fluid stands, as further digestion takes place.

REFERENCES.

1. Hannay, A. J., *Edinb. Med. and Surg. Journ.*, 1833, xl. 65.
2. Mikulicz, *Deutsche med. Woch.*, 1904, xxx. 17 and 50.
3. Zenker and Ziemssen, *Diseases of Oesophagus* in Ziemssen's *Cyclop. of Practice of Medicine*, Lond., 1878, viii. 49.
4. Morell Mackenzie, *Diseases of the Throat and Nose*, Lond., 1884, ii. 115.
5. Rolleston, H. D., *Trans. Path. Soc.*, Lond., 1896, xlvii. 37.
6. Cannon, W. B., *Amer. Journ. Physiol.*, 1906-7, xvii. 429.
7. Mathieu, A., et Roux, J. C., *Pathologie gastro-intestinale*, 1909, i. 78.
8. Myer, J. S., and Carman, R. D., *Journ. Amer. Med. Assoc.*, 1912, lix. 1278.
9. Plummer, H. S., *ibid.*, 1908, li. 549, and 1912, lxviii. 2013.
10. Mathieu, A., et Roux, J. C., *Pathologie gastro-intestinale*, 1909, i. 38.
11. Cannon, W. B., *Amer. Journ. Physiol.*, 1908-9, xxiii. 105.
12. Mathieu, A., et Milian, *Gaz. des Hôp.*, Paris, 1896, lxix. 148.



FIG. 3. Skiagram by Dr. Lindsay Locke, showing dilated oesophagus, filled with opaque meal.

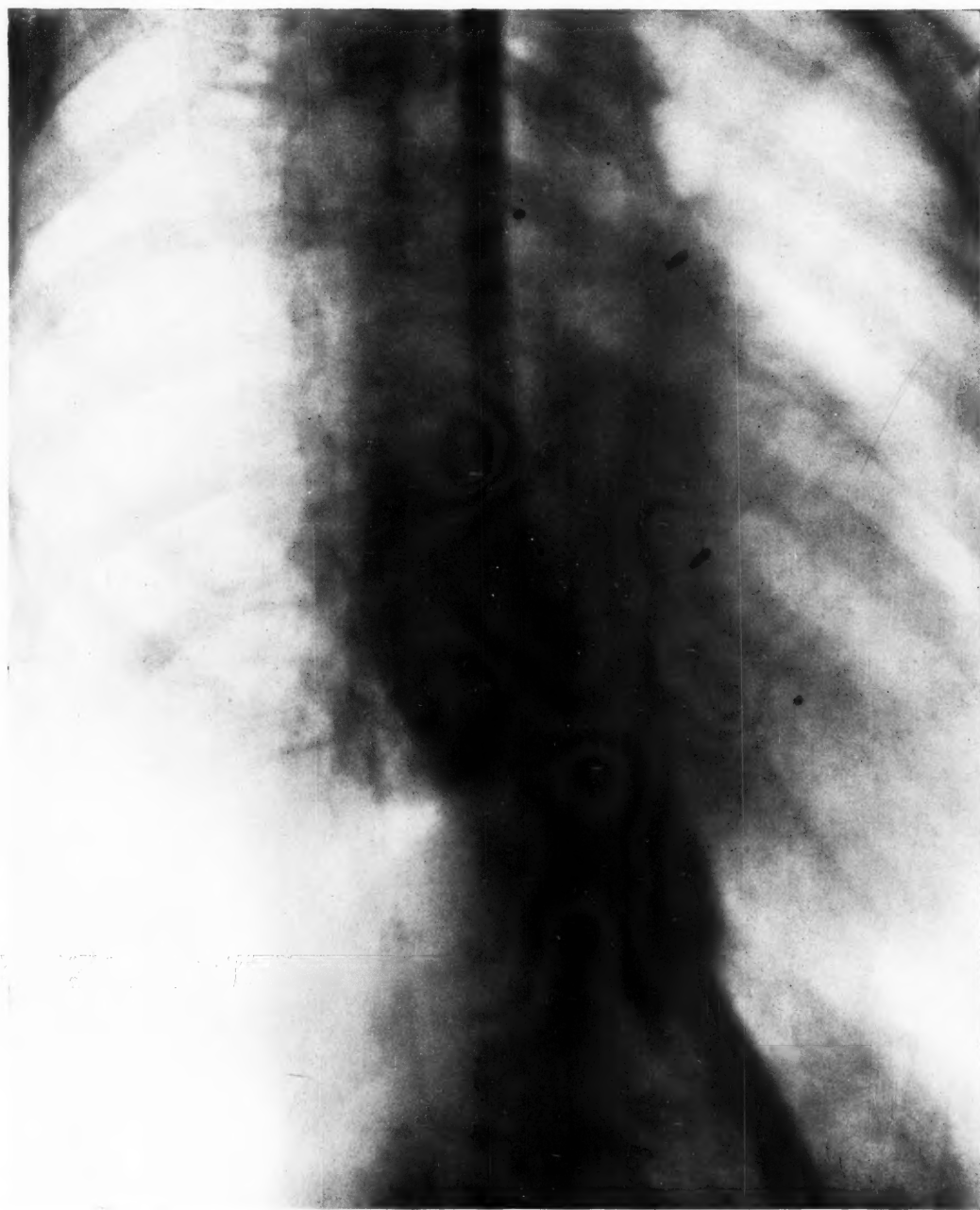


FIG. 4. Skiagram by Dr. Lindsay Locke, taken directly after Fig. 3, showing mercury tube passing through cardia into the stomach.

THE DIAGNOSIS AND SIGNIFICANCE OF GASTRIC HYPERACIDITY

By F. W. ROLPH

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THE methods that have long been in use for detecting free hydrochloric acid in gastric contents by means of indicators were devised at a date when the significance of these indicators was not clearly understood. It is impossible to have an indicator for free hydrochloric acid. Indicators react to certain intensities of acid reaction—to certain concentrations, that is to say, of hydrogen ions. Hydrochloric acid differs from other acid substances or combinations that may occur in the gastric contents, so far as indicators are concerned, merely in the fact that whereas it is almost completely ionized they are very slightly so. If they are present in 100 c.c. in sufficient amount to require 100 c.c. of N/10 soda to completely neutralize them they are so slightly ionized that the concentration of hydrogen ions is not approximately N/10, as would be the case if the acid present and the only acid present was free hydrochloric acid, but not much more than 1/100 or it may be even 1/1000 of this concentration. By judicious use of different indicators it is possible to determine the concentration of hydrogen ions, but not what acids it is that by their dissociation are giving rise to these free hydrogen ions.

When, however, by the use of an indicator it can be shown that the concentration of hydrogen ions is less than, e. g., N/100 or N/1000 it is possible to state positively that the concentration of free hydrochloric acid present is at any rate something less than that: it may be zero. It certainly is not permissible to say that because it requires 20 c.c. of N/10 soda to reduce the concentration of hydrogen ions in 100 c.c. of the fluid to something less than for instance N/1000, therefore there is free hydrochloric acid present equivalent in amount to 20 c.c. of N/10. But this of course is exactly what the use of indicators in the clinical examination of gastric contents has been supposed to establish. The assumption has been implied that no acid but free hydrochloric acid can be present in sufficient amount to give a concentration of hydrogen ions greater than the arbitrarily fixed limit whatever that may be.

The indicator that has been most generally used in fixing this limit is that introduced by Töpfer, dimethylamidoazobenzene, which is red for all con-

centrations of hydrogen ions greater at any rate than $N/1000$. When a gastric fluid gives a red colour with Töpfer's reagent it is said to contain free hydrochloric acid: it is not generally realized that the amount of free hydrochloric acid necessary to give this reaction in the 10 c.c. examined would not be more than at any rate one-tenth of a c.c. of $N/10$: and more important than that, the fact that it is possible even to add 2 or 3 c.c. of $N/10$ soda before the reaction disappears does not show that there is any free hydrochloric acid present. It is possible that there should be present relatively large quantities of an acid sufficiently ionized to give this concentration of hydrogen ions when present in those amounts.

If, for instance, a certain slightly ionized acid, A, present in tenth normal concentration is 1 per cent. ionized and gives therefore $N/1000$ hydrogen ion concentration, the concentration which corresponds to the end reaction of a certain indicator, then in 10 c.c. of a solution containing twice the amount of A or $N/5$ in respect to A the concentration of hydrogen ions would be about $N/500$, and 10 c.c. of $N/10$ soda could be added before the end reaction would be given. But the same degree of acidity, the same concentration of hydrogen ions would be attained if the solution were in respect to the acid A still $N/10$ but at the same time in respect to hydrochloric acid $N/1000$; for the hydrogen ion concentration caused by each of these acids would be approximately $N/1000$ and the sum of these concentrations $N/500$. In this case, however, one-tenth of a c.c. of soda would give the end reaction. In this case, according to current clinical phraseology, the free hydrochloric acidity present would be 1 per cent., whereas in the other case in which there was not any hydrochloric acid at all it would be 100 per cent.

It is clear that in testing for an acid so highly ionized as free hydrochloric acid is, it would be safer to make use of an indicator less sensitive to hydrogen ions than Töpfer's reagent, reacting as it does to a concentration at any rate as low as $N/1000$. An indicator has been used in the examination of gastric contents requiring at least five times this concentration, or about $N/200$, namely, tropaeolin 00. With this indicator about half a c.c. of $N/10$ hydrochloric acid is required to give the reaction in 10 c.c. of fluid. And if there are other weaker acids present in comparatively large amounts, as is usually the case in gastric contents, then of course less free hydrochloric acid than that would be necessary. As a matter of fact in clinical practice too, as will be explained later, it has been found that the information desired is given by this indicator with greater certainty and clearness than by Töpfer's reagent.

But in order to have clear ideas upon the conditions revealed in disorders of the stomach, it is necessary to free one's mind from the idea that there is normally free hydrochloric acid in the gastric contents in appreciable amounts at all.

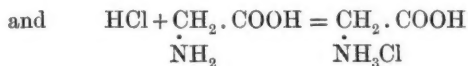
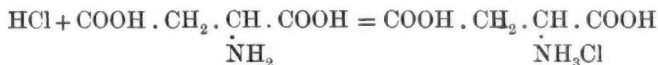
Certain facts may be easily established by such experiments as the following:

1. It is well known that proteins combine with hydrochloric acid: if

a filtered solution of the white of egg be neutralized with acetic acid to phenolphthalein and have some pepsin dissolved in it and then be added to each of a series of flasks at 37° C. containing 50 c.c. of N/20, N/40, N/60, N/80, and N/100 hydrochloric acid respectively, and two drops of tropaeolin 00 solution, and the albumin be added in such amount as is just sufficient in each case to remove the red colour, that is to say, to reduce the hydrogen ion concentration to about N/200 and the maximum conceivable amount of free hydrochloric acid present to a concentration something less than that—if then the flasks are replaced in the incubator after the addition of an equal amount of pepsin (0.3 gm.) to each, at the end of an hour it is found that the red colour has returned in the first three and at the end of six hours in them all.

The combinations of the products of peptic digestion with hydrochloric acid are in this way shown to be more highly ionized than the combination of the albumin with hydrochloric acid. The proteins are known to be compounded of a number of amino acids, the carboxyl groups of which are condensed with the amino groups of their neighbours, and pepsin is known to dissolve this union in many cases. The result of peptic digestion is therefore to liberate the carboxyl groups of a number of amino acids. In this process the number of amino groups capable of binding hydrochloric acid is certainly not diminished; and the increased acidity of the products of peptic digestion can be understood to be due to the greater degree of ionization of the combinations of the digestion products with the hydrochloric acid, to their higher acidity, caused by these liberated carboxyl groups; it is at any rate difficult to see why such hydrolysis should liberate free hydrochloric acid. This experiment has been repeated with other proteins substituted for the egg albumin and in each case with a similar result.

2. In 10 c.c. of N/20 hydrochloric acid, 66.4 mg. of pure analysed aspartic acid were dissolved, an amount, that is to say, equivalent to the amount, half a milligramme molecule, of hydrochloric acid present; the same amount of aspartic acid was dissolved in 20 c.c. of freshly boiled water (it cannot be dissolved in 10 c.c.). Similarly, in 10 c.c. of N/20 hydrochloric acid the equivalent amount of pure glycocoll was dissolved, 37.5 mg., and the same amount also in 10 c.c. of freshly boiled water. We may suppose that combination in each case took place between hydrochloric acid and amino acid according to the equations:



The several solutions were then titrated with NaOH/20 to the following indicators in order: tropaeolin 00, Töpfer's reagent, and phenolphthalein. The results are tabulated thus:

TABLE I.

	0.5 mg. mol. Aspartic Acid.			0.5 mg. mol. Glycocoll.	
	10 c.c. HCl/20.	in 10 c.c. HCl/20.	in 20 c.c. H ₂ O.	in 10 c.c. HCl/20.	in 10 c.c. H ₂ O.
Tropaeolin 00	8.10	5.70	0.0	4.05	0.0
Töpfer's reagent	9.50	11.30	0.10	7.85	0.0
Phenolphthalein	10.00	22.10	10.10	11.25	1.2

From these figures it can be seen that the hydrochloric acid in the presence of aspartic acid cannot have been free even when the end-point to tropaeolin was obtained; for in this case the volume of fluid was 15.7 c.c., and supposing that the soda used had all gone to form sodium chloride and that the remaining hydrochloric acid was all free, that would be 4.3 c.c. N/20 diluted to 15.7 c.c. or N/73, which is nearly three times the hydrogen ion concentration found, if the disappearance of the red colour with tropaeolin be taken as N/200. And as a matter of fact that is about the concentration indicated by the same end-point when 10 c.c. HCl/20 were titrated with 8.10 c.c. NaCH/20 (1.9 c.c. HCl/20 diluted to 18.1 c.c.). When the end-point to Töpfer's reagent is given, more soda had been used than corresponds to the amount of hydrochloric acid present even if that acid had all been free.

Then again with the glycocoll, which it stands to reason is a weaker acid than the dibasic aspartic acid, when the indicator shows the hydrogen ion concentration to be N/200 the concentration of that ion would have been more than four times as great if the hydrochloric acid were free, and when the end-point to Töpfer's reagent was obtained at least six times as great as that indicated. In solutions of amino acid with equivalent amounts of hydrochloric acid combinations are formed that are ionized considerably less than the hydrochloric acid would be if free, but more than the amino acids themselves would be.

In disorders due to 'hyperacidity' of the gastric contents, on titration of the contents obtained after a test breakfast I have invariably found that they react with tropaeolin 00 so as to give a red colour and that a greater or less quantity of soda is required to remove this red colour. In other words, the symptoms of hyperacidity are present when the hydrogen ion concentration of the gastric contents is higher than N/200. In the contents removed from the stomach when there are no clinical symptoms of hyperacidity I have never found such a degree of acidity as this—never, in other words, a red colour on testing with tropaeolin 00.

In the light of the experimental results recorded above we must say not only that the stomach contents one hour after the test meal do not normally contain free hydrochloric acid, but that even when the contents are abnormally acid there is no ground for saying that hydrochloric acid is free.

It is of course a point of no practical importance, and hardly even of academic interest, whether in any particular case hydrochloric acid can be free or not. The question that it is material to decide is how acid the contents are,

and how acid they may be without causing discomfort or inconvenience. It is possible that some indicator other than tropaeolin 00 may be found that sets the limit to the acidity that can be tolerated more exactly than this indicator does. But there is no question whatever that this limit cannot be determined by titrating with Töpfer's reagent. A reaction to this or any indicator shows a certain degree of acidity, but the amount of soda required to give the end-point with an indicator does not and cannot show how much more acid the fluid is than the end reaction, the concentration of hydrogen ions at which the indicator turns. To decide this other indicators turning at higher concentrations must be used, or else the nature and degree of ionization of the acids titrated must be known, which is obviously not possible. Töpfer's reagent indicates a degree of acidity that is found normally in the contents of the stomach one hour after the test breakfast, and the fact that 1 c.c. or 6 c.c. of the soda is required to give the end-point to this indicator in 10 c.c. tells one nothing of the actual degree of acidity, certainly not how much greater it really is than that indicated by the end-point.

The following cases, which are typical of a large number that I could quote, serve to illustrate this point. In each case under (a) are given the number of c.c. necessary to give the end reaction to tropaeolin 00, under (b) to Töpfer's reagent, under (c) to phenolphthalein in 100 c.c. of the filtered contents.

Case I. Woman, aged 27. Only gastro-intestinal symptoms, constipation, poor appetite, and flatulence. No symptoms of hyperacidity. Diagnosis, neurasthenia.

(a) 0. (b) 45. (c) 78.

Case II. Woman, aged 28. Pain in epigastrium half an hour after meals, heartburn, acid eructations, has vomited blood. Diagnosis, gastric ulcer.

(a) 9. (b) 19. (c) 32.

Case III. Man, aged 26. Pain in epigastrium three hours after eating, relieved by food or alkalis, heartburn, vomiting of sour fluid. Diagnosis (operation), duodenal ulcer.

(a) 60. (b) 79. (c) 91.

Case IV. Woman, aged 35. Epigastric pain and heartburn one hour after meals, relieved by alkalis. Diagnosis, nervous hyperacidity.

(a) 18. (b) 28. (c) 60.

Case V. Man, aged 30. Symptoms of gastric hyperacidity extremely marked. Diagnosis, gallstones or duodenal ulcer.

(a) 35. (b) 52.5. (c) 75.

After ten days in bed with gastric lavage, alkalis, &c., the symptoms entirely disappeared and the test-meal reading was then:

(a) 0. (b) 44. (c) 70.

In Case I, and in Case V after treatment, the 'free hydrochloric acid' as estimated by Töpfer's reagent was high, but there was no tropaeolin reaction and no symptom of hyperacidity; in Cases II and IV it was low, or not high, and the

tropaeolin reaction and symptoms were pronounced. In Case V the treatment left the 'free hydrochloric acid' high, but removed a strong tropaeolin reaction and the symptoms completely.

It should be noted that the use of relatively large amounts of soda to reach the end reaction to tropaeolin 00 may be significant in a way that cannot hold for Töpfer's reagent. It is perfectly true, of course, that with tropaeolin the use of a large or a small amount of soda does not indicate how much greater the acidity is than that indicated at the end reaction with the indicator, just as has been argued above against the common method of using of Töpfer's reagent. But then Töpfer's reagent gives a reaction which is found normally in the gastric contents, whereas any reaction with tropaeolin is abnormal and the amount of acid with a higher acidity than is normal is a measure of how much it will take to correct the defect and give relief. And it may, so far as is yet known, not make a different clinical picture if the acidity is much or little higher than that indicated by any reaction with tropaeolin.

I am convinced from such evidence as this, and these are only a few out of a large number of cases, that there is a connexion between the symptoms of hyperacidity and the concentration of hydrogen ions in the gastric contents; such quantities of highly ionized acid combinations cause disturbance when larger quantities of less ionized do not, and there may be little or much acid found on titrating with an indicator such as Töpfer's reagent, without that revealing whether there is anything abnormal or not. In either case the hydrogen ion concentration may or may not be as high as $N/200$, and it is only when it is as high as that that trouble is experienced.

The questions then arise—what are the acids that are sufficiently ionized to give this concentration, and why do they occur in the patients who suffer in this way and not in the normal subject? The question whether the offending acid is free hydrochloric acid or not cannot, of course, be decided with certainty; but the experiments already mentioned show that combinations of known amino acids with hydrochloric acid are capable of giving the reaction, and also that in the course of digestion of proteins by pepsin, whether these particular amino acids are or are not set free in gastric contents, combinations do occur which fulfil the conditions.

Those experiments show that the dibasic acid, aspartic acid combined with hydrochloric acid, is, as might be expected, more highly ionized than the monobasic acid glycocoll under the same conditions. If, therefore, in the hydrolysis of proteins by pepsin, conditions occur which favour the occurrence of the cleavage in those positions in which it will liberate the carboxyl groups of the dibasic acids, aspartic or glutamic, rather than in positions in which monocarboxylic amino acids are liberated, then under those conditions the products would be more highly ionized, that is to say, more intensely acid. The only conditions that we know of in which pepsin would be likely to do this depend upon the nature of the protein. Some proteins, notably those found in cereal grains, but in a less degree casein, contain a large amount of their nitrogen in the form of

dibasic glutamic acid. The gluten and gliadin, indeed, of wheat contain more than half their nitrogen, so far as this has been traced to identified substances, in this form. An experiment was planned to test whether the acidity of the products of digestion of different proteins by pepsin varied in accordance with the amount of glutamic acid that the proteins yield. Such an amount of each five proteins as contained 0.1095 of nitrogen was treated with 100 c.c. of N/20 hydrochloric acid and 0.3 gm. of Merck's pepsin in five flasks in the incubator. After thirty minutes, one hour, four hours, and twenty-four hours, 20 c.c. were removed from each flask, filtered, and 10 c.c. of the filtrate titrated with N/20 soda, using in each case the same three indicators as in the former experiment.

The casein was prepared according to Hammarsten; the meat powder was prepared by drying and powdering ventricular muscle of the calf freed from the pericardial fat; the wheat proteins were introduced simply in the form of flour.

TABLE II.

Kept at 37° C. for	Indicator.	No. of c.c. of NaOH/20 to give end reaction in 10 c.c. of digestion products from:														
		Casein 0.752 grm.			Flour 5.103 grm.			Egg albumin 21.10 c.c.			Meat powder 0.795 grm.			Edestin 0.600 grm.		
		(a)	(b)	(c)	(a)	(b)	(c)	(a)	(b)	(c)	(a)	(b)	(c)	(a)	(b)	(c)
30 min.	(a) Tropaeolin (b) Töpfer (c) Phenolphth.	1.2			1.1			0.0			[6.0*]			0.0		
		5.3			4.3			6.8			[8.2*]			9.3		
			6.0			4.8			7.9			8.9			10.2	
1 hour	(a) Tropaeolin (b) Töpfer (c) Phenolphth.	2.6			2.3			0.0			3.5			3.5		
		5.7			7.3			5.9			7.5			7.2		
			13.4			13.2			10.0			11.3			11.6	
4 hours	(a) Tropaeolin (b) Töpfer (c) Phenolphth.	3.8			3.8			1.0			5.1			4.6		
		5.7			7.3			5.6			7.9			7.5		
			15.5			13.7			10.6			11.4			11.9	
24 hours	Tropaeolin (b) Töpfer (c) Phenolphth.	3.8			4.7									3.5		
		5.8			7.8									5.1		
			17.1			15.3									12.0	

* These figures are accounted for by the fact that the comparatively coarse meat powder had not got sufficiently dissolved to allow the protein to combine with the hydrochloric acid.

The results are given in Table II. They illustrate in the first place the point brought out in the earlier experiments described above, that the hydrolysis of the protein liberates groupings which in combination with hydrochloric acid are more highly ionized than the combination of the protein itself with the acid. In the case of edestin after four hours' action the total combining power of the acid products hardly changes (column 5 (c)), while the amount of acid strong enough to react to tropaeolin and even to Töpfer's reagent actually diminishes after that period. In the case of the other proteins there is generally speaking a tendency not only for the amount of acids ('total acidity' column 1) to increase, but for the amount of stronger acids (columns (a) and (b)) to increase in

proportion to the total acids. This is most noticeably the case with the wheat protein, while with egg albumin this is not to be observed. As a matter of fact it is the wheat proteins that of those studied contain much the largest amount of the comparatively strong dibasic acids, in this case glutamic acid. More than half of the nitrogen in the gluten and gliadin of wheat that has been traced to identified substances occurs in the form of glutamic acid. This fact may possibly account for the relatively large amount of acid digestion products giving a high hydrogen ion concentration.

But while the amount of the more strongly acid products yielded by wheat proteins bears out such an idea, in the case of the other proteins tested the amounts do not very closely follow the differences in the several yields of dibasic amino acids obtained from them; it may be too much to expect that they should, as the data with regard to the composition of the proteins, especially in the case of egg albumin, are too fragmentary.

It must therefore be confessed that we cannot as yet do more than speculate on the explanation of the hyperacidity in disturbances of gastric function. The influence of vagotonia may be called in to help; and the association of recognized symptoms of this condition with hyperacidity which I have frequently noticed may possibly point to this explanation.

Whatever the true explanation may be, the symptoms of hyperacidity go with a concentration of hydrogen ion in the gastric contents after a test meal which is indicated by a reaction with tropaeolin 00, and is never given when those symptoms are absent; and the presence or absence of this degree of acidity cannot be determined by titrating the amount of acid that gives the reaction to Töpfer's reagent.

SCLEREMA NEONATORUM

By W. S. PATERSON

IN the conditions, or group of conditions, commonly associated under the name 'sclerema neonatorum', features of special interest are that the disease is one of comparative rarity, and that very little as to the causation is yet definitely known.

Although it has attracted the attention of many observers, their conflicting views have tended to perplexity rather than to the formation of a clear picture. This is reflected in the multiplicity of names under which various writers have described the disease. From the time that Usembezius published the first known report, many descriptive terms have been added to the nomenclature. Those which for a time received recognition include the following: *scleroderma neonatorum*; *scélérème des enfants*; *oedématie concrète*; Thirial's disease; *algor progressivus*; *induratio telae cellularis*; *induratio telae cellularis neonatorum*; *algidité progressive*; *l'endurcissement athrepsique*; *Sclerom der Neugeborenen*; *mal de mâchoire*; *trismus des nouveau-nés*; *hidebound*; *scleroma*; *sclerisma*; *sclerema*; *oedematia*; *stagnosis*; *chorionitis*; *scleroedema*. In later years this complexity of titles has been simplified by the recognition of two allied conditions, viz. *sclerema neonatorum* and *oedema neonatorum*, with, possibly, the existence of a third state, the so-called *pseudo-sclerema neonatorum*. My attention was specially drawn to this disease from having the opportunity of observing a case in my own practice. In this instance, while I consider that the diagnosis of *sclerema neonatorum* was established, there were absent some of the features usually attendant on that condition.

On reference to various text-books (both on diseases of the skin and on diseases of infancy) it is notable that most writers dismiss the condition briefly. There is a general unanimity in describing *sclerema neonatorum* as a disease found to be present at or shortly after birth, usually in weakly infants, most commonly in those born in unfavourable surroundings; as characterized by progressive induration of the skin and adjacent tissues, and as, with subnormal temperature and slow heart, usually terminating fatally within a few days.

In the case which came under my observation the first indications of disease were noticed thirteen hours after birth, the condition was fully developed within seventy-two hours, the induration was almost general over the body, and it corresponded in its main features with the published descriptions. In regard to the circumstances of a well-developed child in a favourable

environment, and also in a successful issue, the case did not agree with the usual reports, and for these reasons I decided to add my contribution to the subject.

Historical Outline.

The most satisfactory account of the earliest recognition of this disease was given by Parrot of Paris in 1877 in his lectures on 'L'Athrepsie' at the Clinique des nouveau-nés. It is to him that we are indebted for pointing out the distinction between two conditions somewhat allied and, until then, frequently confused, viz. 'sclerema' and 'oedema' neonatorum, and it is from his account that I have drawn most of my knowledge of the historical aspect.

The first recorded case was that of a child born in the Stockholm Hospital in 1718; it was said to have been born prematurely and to have died six hours after birth. It was recorded by Usembezius of Ulm in *Ephemerides Acad. Cæsareo-Leopoldinae naturae curios.* (December, 1718) under the title of 'Partus Octimestris, Foetus Vivus, Frigidus et Rigidus'. This was evidently an instance of congenital sclerema, and Parrot refers to the writer's artless suggestion that it was due to maternal impression, as the mother, during her pregnancy, had spent much time contemplating ecclesiastical statues! In 1732 reference to this case was also made by Schuringius in his *Embryology* ('De Foetu frigido et rigido'), and he described the infant as being 'from head to foot like a piece of smoke-dried meat'. This interesting observation was quoted more than once, but the affection to which it referred was almost completely ignored for many years until Denman, Professor of Midwifery at the Middlesex Hospital, directed attention to it in his lectures, and this formed a starting-point for work by Underwood of the London Lying-in Hospital. In 1770 Underwood published his *Treatise on the Diseases of Children*, and therein made the first valuable contribution to the study of this disease. Under the name of 'hidebound disease' it there received description, clinically complete and accurate, as an induration of the subcutaneous tissue. The chief points to which he drew attention were the following: the disease is usually found in the children of poor people, particularly in those suffering from an obstinate intestinal ailment where the excreta have been like wax or clay; it is not usually found immediately after birth but it generally appears within ten days; the first indication is the alteration in the colour and consistency of the skin, which becomes like soft wax; then the tissues become hard and resistant to the touch, but without oedematous pitting on pressure; thereafter there is progressive increase of the hardness, both in superficial area and in density, so that the skin cannot be pinched up or slid over the subjacent muscles; even the sheaths and fibres of the muscles may be affected, the rigidity being most marked on the face and extremities, but the muscles of the lower jaw are the only ones which become completely fixed; if convulsions occur, they do not affect the extremities; the child is always cold, and there is a characteristic moaning cry, often feeble, and quite unlike the cry of an ordinary child of the same age; though he may survive for some days longer, he seems constantly to

be at the point of death. On autopsy, the author had never found any fluid in the cellular tissue; he considered the proximate cause of disease to be a spasm of the skin, and the remote cause an unwholesome atmosphere.

Then arose confusion. Andry of Paris read Underwood's description and thought it referred to a condition of which he had some cases in the Hospice des Enfants Trouvés. To this affection which, from its supposed incurability, had received little attention, and which actually was oedema neonatorum, he gave the name 'sclérème', and published his account of it. In this he stated that the extremities, especially the thighs, are increased in size from infiltration in the cellular tissue; the soles of the feet and the pubic region are swollen, red, and hard; suppuration might rarely occur, mortification more frequently, and that, on autopsy, serous effusion is always to be found in the cellular tissue, the fluid being coagulable by heat.

Though Underwood recognized the clinical differences between his own cases and those described by Andry, it was supposed that the variation of type might be due to climatic conditions in London differing from those in Paris.

Andry's error was repeated by others, and contributions by Capuron, Auvity, Chambon, and Léger all perpetuated the confusion between sclerema and oedema, and they united in including the oedema under the name of 'endurcissement du tissu cellulaire'. A contribution by Denis would suggest that he had in some measure appreciated the error of previous writers, inasmuch as he subdivided the 'endurcissement du tissu cellulaire' into two varieties, serous or oedematous, and fatty or solid, but his further conclusions did not assist progress. He considered that the two varieties presented the strongest analogy in respect to their symptoms, their progress, and their termination, while the differences were unimportant in the colour of the skin, the consistency of the tissues, and the fact that the cellular tissue in the one case was infiltrated with serum and in the other laden with fat.

Billard recognized two varieties of induration and gave a clear description of oedema neonatorum, but he considered the true sclerema as a condition found after death, or, at the earliest, in infants actually at the point of death.

Valleix spoke of 'fatty induration' as being entirely different from the oedema, but, along with Billard, he considered the former to be a post-mortem change.

Bouchut added another complication by insisting that this condition is not peculiar to the new-born, that it is, in fact, the same disease as scleroderma. According to him, it is unjustifiable to differentiate between the two varieties, simple and oedematous, the oedema being only a consequence of the primary induration; although he claimed that the induration was the essential lesion, he gave no detailed description of it, stating only that it was necessarily a condition of the moribund state. In brief, while attempting to describe 'sclerema or induration of the skin of the new-born', Bouchut really described a non-existent type of disease.

In 1873 Clementowski of Moscow published a contribution (*Oesterr. Jahrbuch*

für Pädiatr.) in which he distinguished three varieties of sclerema, viz. the erysipelatous, the oedematous, and the adipose. The first referred to the subcutaneous serous infiltration often found with erysipelas of the new-born; the second was oedema neonatorum; and his description of the third was applicable quite as much to cadaveric rigidity as to any type of disease.

I have quoted points from some authors to indicate the utter confusion which, for many years, blinded many observers in the actual recognition of the disease. Andry's original mistake in applying Underwood's description of one affection to another and distinct morbid condition was followed by other writers, not only those above mentioned, but some in Britain—Coley, West, and others—and most of the German authorities. This state of affairs continued until Parrot emphasized the clinical and pathological lines of demarcation between the two maladies and, for the first time, offered a rational appreciation of the situation.

His example was followed by Henoch of Berlin, who in 1881, in his lectures on diseases of children, differentiated clearly between sclerema and oedema.

That this recognition did not receive universal acceptance is demonstrated by the fact that, for years afterwards, in various standard works, even in those devoted to diseases of children, the writers were content to ignore these ailments or to describe them in such a manner as to show that the confusion still existed. The fullest account in English is that by Ballantyne, while contributions by other observers—Barrs, Langmead, Money, and others—have, for the most part, been in the form of extended notes of individual cases.

General Considerations.

It has been recognized that the disease is most likely to be found where there are general conditions inimical to health. Immaturity at birth, congenital weakness, congenital syphilis, illegitimacy, parental poverty or maternal debility, and also the occurrence of birth during very cold weather, have all been taken as factors in individual cases, but we are still without positive knowledge of the exact cause. Ballantyne holds that there is no proof of direct association with congenital syphilis, but he claims that 'probably the diseased process is initiated *in utero*'. It may be mentioned incidentally that, in the case which I have to report, samples of blood from the child's parents were examined for me, the Wassermann test in each case being negative.

To give some explanation of this comparative ignorance of a much discussed condition, two points may be mentioned. One is the actual rarity of the disease (although Osler suggests that it may be much more common than statistics would indicate), so that few opportunities are afforded for its study. The second point is that, even when the disease does occur, it may probably be in surroundings which are not favourable for careful examination by any competent observer. A disease which is so commonly and so soon fatal, occurring in a premature or illegitimate infant, perhaps born into poverty-stricken or squalid surroundings, or amidst adverse climatic conditions, might easily fail

to be recognized: death would be ascribed to the other obvious disabilities, and the brawny induration might be noticed only after death, and be then supposed to be post-mortem rigidity.

Further, it is also probable that mild cases may occur and may become well without being recognized. Garrod refers to the occasional observation at out-patient dispensaries of infants, generally of a few weeks old, having localized areas of induration with all the characters assigned to sclerema. In these cases the prominent symptoms had passed off, and he (Garrod) had had to watch only the gradual resolution of the sclerematous lesions, a process, in his experience, usually lasting five or six months. He considers that such cases, if true sclerema, are less rare than the fatal cases.

In this limitation of our knowledge, it is impossible to give a comprehensive definition of the disease, its cause, its variations, and its characteristics. Ballantyne offers a provisional definition which may be taken as reasonable, viz. 'a rare disease occurring most commonly in the new-born, characterized by induration of the subcutaneous tissue, and little amenable to treatment'. He expresses the opinion that, without fuller knowledge of the pathological and physiological processes concerned, a more scientific definition is impossible.

Parrot states that sclerema is one of the signs of athrepsia, and that athrepsia is only a complication of oedema neonatorum; this opinion, as I hope to show, does not appear to be justified. He says, 'The induration under the influence of athrepsia takes possession of these parts for which it has affinity and expels from them the serous fluid with which it cannot co-exist. One cannot give a better proof of the incompatibility of the two affections. One displaces the other because they can never exhibit themselves together in the same situation.'

In his clear differentiation between the two conditions, 'sclerema' and 'oedema' of the new-born, Parrot gives a graphic picture of the former condition, and it seems fitting, although the quotation is somewhat lengthy, to give here some parts of the full description given by him:

'When the disease (athrepsia) develops slowly, there may be two very different results which I wish you to recognize, without its being possible for me to state precisely all the circumstances which determine the one rather than the other. In the one case . . . In reference to the other condition, it constitutes the athreptic induration. We notice this specially when the disease assumes a subacute form almost immediately after birth, in subjects of moderate plumpness. The skin, far from forming folds, becomes, on the contrary, stretched and its surface becomes remarkably smooth; it loses all flexibility, and it is absolutely impossible to separate it from the subjacent parts, with which it seems to be very closely united. This alteration begins in the lower limbs; the lumbar region is then invaded, then the lower part of the trunk, and finally the whole body, the face included. Daily one may see the tension and the hardness of the skin make progress, and soon, on touching it, one has the feeling which thick

leather gives. It appears as if all the soft parts were coagulated, and as if one had before his eyes a figure of wood or marble; therefore the first observer who saw an infant affected in this way imagined guilelessly that the mother had gazed at a statue. The integument is not to be pitted by pressure of the finger, and its colour becomes faintly bluish or livid. Immobilized by this rigid condition, which cannot be overcome spontaneously, the limbs remain extended, and, but for certain movements of the thorax and face which one still observes, one might believe that the body is in a state of cadaveric rigidity. Dugés reports that on grasping below the head infants thus affected, he was able to hold them in a horizontal position, as if they had been made in one piece only. It has often happened to me to make the same experiment in another fashion; by applying the radial border of my hand under the back of the little invalid, I have held him up as if he had been cast as a rigid shaft. When the face is invaded the stiffness of the lips, of the sides of the cheeks, and of the muscles keeps the mouth closed and renders sucking and swallowing impossible. Thus one understands how a certain number of observers from the time of Lodmann, quoted by Denis, until our own day, have believed that they had to deal with the affection called "lockjaw" or "trismus of the new-born". . . .

'This induration of the new-born, where the muscles and the cellular and fatty tissues are all affected as much as the skin, is invariably the result of athrepsia. I have never seen this develop apart from it. . . .

'In the latter days of athrepsia, the peripheral soft parts diminish, dry up and harden; the skin becomes stretched and assumes a livid colour; the whole body becomes rigid, immobile, and seems mummified. This characteristic condition is only met with in athrepsia, and hereafter I shall call it by the name of "endurcissement athrepsique des nouveau-nés". Of the posture I have only a few points to mention to you. . . . The state of the limbs is generally as follows: the thighs are drawn up to the trunk and the legs are bent upon them; the toes are sharply bent towards the sole of the foot as if there were an actual contracture; the arms and forearms are stretched, but the wrists are flexed on the latter, and the fingers bent into the palm of the hand about the thumb. One must use some force to overcome the flexion, and when one has straightened out these parts, one sees them quickly return to their former position. These movements, furthermore, provoke but little pain, and some infants bear them without arousing from their stupor. . . .

'The skull undergoes some important modifications. Its size becomes less, as is proved by the condition of the osseous portions which form the vault, and by that of the soft parts which unite them. The projection which the fontanelle causes in health gradually sinks down, and in its place one may see an actual hollow, the depth of which may reach three or even four millimetres. The diameter of this membranous surface also decreases in a very notable fashion by the approach of the bones which surround it, and in some patients it disappears almost altogether.

'At the same time, as M. Bouchaud was the first to observe, the sutures

become fixed by the disappearance of the interosseous spaces. The bones first draw together, then override, in such a manner as to form linear projections. These, always appreciable to the touch, can also be proved by sight in many cases, where the phenomena, well marked, become more obvious by the thinning of the hairy scalp and by its stretching over the calvarium. . . .

'When the induration extends also to the face, one might say that a stiff mask covered it and there is no visible movement. The jaws, clenched on one another, cannot be opened without force, and if one happens to separate them, they come together as if moved by a spring. Add to this the pained expression, and you will have all the characteristics of the athreptic physiognomy.'

I have thought it of value to incorporate these portions of Parrot's description of sclerema. They are not taken consecutively, but they serve to illustrate some of the appearances which I have not seen described elsewhere. I have omitted parts which seemed applicable to his conception of 'athrepsia' in general rather than to sclerema in particular.

In another place, Parrot quotes a description by Denis which also seems worthy of repetition:

'The indurated parts of the body are neither elastic nor doughy; from the effects of the disease they have acquired the firmness of suet. The skin, of a yellowish-white colour, has the appearance of leather; it does not slip over the subjacent muscles, and one may feel under it, here and there, very firm masses. When the subject is in the third stage of induration one might believe that it had undergone freezing; on percussion, the limbs sometimes give the sound of wood. The coldness is intense, the movements difficult; trismus and the other nervous phenomena are less common than in the oedematous variety; the respiration, the circulation, and the digestion are also less disturbed. All these phenomena are attributed to the accumulation of the cellular fat in the vesicles, and to the increase of its density.'

Some consideration must be given to the possible concurrence of oedema and sclerema. Parrot contended that these two conditions were 'not only different but, so to say, opposed', and his claim that the two could not be co-existent was in accordance with the views held by some of the more accurate clinicians, but in more recent years there has been a tendency to recognize an indurative and an oedematous variety of sclerema. G. Somma recognizes three varieties of sclerema, viz. 'indurative', 'oedematous', and 'mixed', according to the state of the subcutaneous tissues, and Ballantyne indicates his acceptance of the statement that oedematous infiltration may occur in sclerema. Finkelstein, in the *Lehrbuch der Säuglingskrankheiten* (1908), says that in some cases sclerema and oedema may be associated together, and the oedema may be so bad that pitting on pressure may scarcely be got, so that diagnosis during life may not be possible.

I would suggest that in those cases where serous infiltration is found it may be considered, not as an essential feature of sclerema nor characteristic of any special type of the disease, but only as a secondary sign. This idea is corro-

borated by the fact that cases of sclerema have been found with serous effusion into the peritoneal or pericardial cavities, and in others there has been oedema of the epiglottis and vocal cords.

In the more recent literature to which I have had access I have not found many other points of importance in regard to macroscopic features. Mensi in the *Rivista di clinica pediatrica* (1911) had an article on 'Lo sclerema di neonati', of which an abstract is given in *Zeitschrift für Kinderheilkunde* (1911). From personal observation of eighty-two cases, he recommends the differentiation of sclerema into two types, according to the appearance of the skin. The first occurs in premature and newly-born infants and in the cold season of the year; it follows a previous oedema, and the induration appears first in the buttocks, never or seldom in the hands and feet, and it spreads more or less over the body; the temperature is usually low, seldom febrile; common complications are broncho-pneumonia and nephritis, and the disease usually ends fatally. On autopsy, the skin is found to be atrophied, with absence of the granular layer, the cells of the cutis are closely packed together, and there is dilatation of the vessels with haemorrhages into the cutis.

The second type is characterized by condensation, thinning, and drying of the skin; it occurs less often in premature children, mostly in warm weather, and it may begin with oedema; it also begins in the buttocks and may become general. Usual complications are diarrhoea and fever, causing death. On examination post mortem, there is found to be atrophy of the dermis, with condensation of the fibres, scantiness of the cells and vessels of the skin, and abnormal development of fibrous tissue round the fat. Mensi considers that the first type corresponds to sclerema neonatorum, and the second to sclerema adiposum of Parrot. The large number of cases which Mensi claims to have seen would raise some doubt as to whether they were all true cases of sclerema neonatorum.

In the matter of temperature some very striking records have at times been made, confirming the general observation of subnormal temperature as a common feature in this condition. Henoeh makes note of temperature as low as 83.3° F., Verson records one of 79° F., while Roger had one case even as low as 72° F.

Depression of the temperature, however, is not an invariable sign, and in other cases a greater or less degree of pyrexia has been found present, at least for part of the currency of the illness.

Another variable manifestation is in the coloration of the skin. 'Ivory pallor', 'dirty yellow' or 'waxen appearance', and different tints of bluish, purplish, or livid colour have been mentioned in the description of some cases, while in others, again, no change from the normal colour was to be recognized. Henoeh reports that almost all of his cases were more or less jaundiced.

Other points referred to by some writers are the facts that in sclerema there are not found any of the changes in the urine which are characteristic of oedema, and also that in sclerema the lax tissues of the eyelids and of the

scrotum or the labia majora are not liable to be affected and swollen as in oedema.

In the *Lancet* Carpenter published a report of a successful case under his care in the London North Eastern Hospital for Children. He refers to the rarity of the disease and to its being even less common in England than in France and Italy. He also states that there are 'two disorders, differing at any rate in degree, which both go under this name' (i.e. sclerema neonatorum). The more common type occurs in children otherwise normal; it is limited to the skin and subjacent tissues, and it usually ends in recovery. The second type attacks weakly or premature children, and it is accompanied by severe disorder of the alimentary, respiratory, or renal systems, ending commonly in death.

In the case described by him the child was six weeks old, well developed and apparently normal except for the cutaneous induration on the posterior aspect of the body, the back of the scalp, neck, trunk, buttocks, arms, and thighs being all affected. In these regions the skin was of a pink-purplish appearance with well-marked dimples and slight rounded eminences. On pressure with the finger no pitting occurred, but the colour faded to white, and it slowly returned when the pressure was removed. These areas ended by gradual thinning and they were not painful. At a later stage the induration extended to the angles of the jaws, the sides of the neck, and down the arms, with islets all over the abdomen and chest. Examination of the blood was inconclusive, the relative proportions of the various corpuscles given by him being quite within the normal limits found in infancy. A small piece of skin and subcutaneous tissue was excised from the thigh for examination and, macroscopically, the fat appeared distinctly whiter, much harder, and in larger globules than normal. Microscopically, no definite abnormality was found, the serous infiltration and increase of connective tissue sometimes described being definitely absent in this case. The gradual progress of the case was slow and irregular and, after five months' observation, there were patches of induration still present.

In addition to these general considerations about sclerema, it is desirable to make brief reference to some conditions which may reasonably be linked with it, and in which there might be difficulty in the differential diagnosis. Of these, *oedema neonatorum* is the most important, if for no other reason than the fact that the two conditions have so frequently been mistaken for each other.

Oedema neonatorum is to be regarded as a sign of disease rather than as constituting in itself a definite and self-existing condition. It is found usually if not invariably in association with other recognizable affections, renal, pulmonary, cardiac, or intestinal, such as those which commonly cause oedema in adults, and its distribution is, as one might expect to find it, in those situations where the influence of gravity or the laxity of the tissues would be most favourable to its occurrence.

In one case recorded by Ballantyne the child (male) was born while

the mother was suffering from acute bronchitis with pneumonic patches; within a few hours after birth he developed marked oedema, with suppression of urine, and died in two days; on section, there was found tubular and glomerular nephritis; in this case the condition may reasonably be ascribed to the maternal toxæmia.

The most important feature distinguishing it from sclerema is the presence of serous fluid in the interstices of the subcutaneous tissue. This will in nearly all cases allow of pitting on pressure, though it is possible that in an extreme case the infiltration may be so firm that pitting may not be got at all.

The presence of oedema is always to be held as a grave omen, and such cases usually end fatally. Kaposi suggests that the proximate cause is the retardation of the capillary circulation, caused remotely by systemic disease or by extreme weakness. After death, whatever the pathological findings as to the primary disease, there will always be found the characteristic serous effusion in the subcutaneous tissues, and microscopic sections, which, from the looseness of the tissues are not easily made, will show bundles of fat cells, loosely connected by thin bands of fibrous tissue.

Syphilitic roseola might conceivably give trouble in diagnosis from sclerema, but in such a case, apart from the actual appearances, the other facts of the history, the Wassermann reaction, and the results of anti-syphilitic treatment would serve to establish an opinion.

Tetanus neonatorum, another rare condition, might need consideration as a possible alternative to the diagnosis of sclerema. If due to the earliest possible infection, as from inoculation of the raw surface of the umbilical cord, it might develop within eight or nine days. The first indication would probably be trismus, and then would follow other signs of muscular spasm rather than of subcutaneous induration; the rigidity would be greater than in sclerema, and the temperature curve would be different from that found in sclerema.

Erysipelas neonatorum may also arise from umbilical infection or from a mother with puerperal fever. It usually occurs within ten days after birth, and it presents the features of continuous pyrexia, and the blush, with its sharply defined and advancing margin, without any material difference from the usual indications of erysipelas.

Fat-sclerema is another of the class of symptomatic conditions, and it may be found in young infants where there has been marked drainage of fluids from the body, as from severe vomiting or diarrhoea. It occurs after death or, occasionally, just before it, and it is supposed to be due to solidification of the panniculus adiposus.

Description has also been given of a condition called '*pseudo-sclerema*', but it is open to question whether this ought to be considered as having any essential pathological difference from true sclerema. The general account of it is that this is a condition resembling sclerema neonatorum, but where the signs are less marked, and where the disease does not end in death. This description may be paraphrased, not unfairly, by saying, 'if it is a bad case and the child

dies, it is a true sclerema, while if the condition is less severe and the child recovers, it is a pseudo-sclerema'.

In the absence of full knowledge and while the aetiology is mainly speculative, it seems to me more reasonable to hold that the two conditions, sclerema and 'pseudo-sclerema' so called, are essentially the same, and that the differences in the signs and the result are dependent on the individual child itself, on its own vitality, and its degree of resistance.

Due regard must be given to the statement of Henoeh that infants affected with sclerema 'invariably die'. One is reluctant to traverse, perhaps on inconclusive grounds, any statement made by one of his wide experience. And yet, such an observation, although it is the honest opinion of a careful clinician, is obviously gained from his own experience, and in regard to a disease such as the one under review the limited possibilities of studying the affection must be remembered. It is also pertinent to remember comparable opinions by others of equal eminence in their own spheres, where fuller knowledge has proved their inaccuracy. It would need no laborious 'delving into the musty records of a bygone past' to find competent surgeons who held definitely that the opening of the peritoneal cavity must inevitably and invariably cause death, and now, within the space of one generation, laparotomy has become almost a commonplace of surgical procedure.

From the preceding it is, in my opinion, reasonable at this stage to draw some general conclusions on the subject, and these may be summarized as follows:—Sclerema neonatorum is to be recognized as a well-defined disease, not necessarily associated with or secondary to any other recognizable morbid condition; it may present conditions varying widely in degree as to the extent of the local lesions, the severity of the constitutional symptoms, and the gravity of the ultimate prognosis; further, these conditions will vary inversely as the degree of individual resistance, and possibly may vary directly as the degree of infection by the primary cause; and, finally, the differentiation of cases into true and false types of sclerema is not based on any sound or scientific premisses.

Personal Observation.

In the two cases of which I have had the opportunity of personal examination, the first is of special interest in regard to the apparently favourable condition of the child, and also in demonstrating that widespread development of the induration and severe constitutional symptoms are not necessarily followed by death.

This case occurred in a household which has been known to me for some years, and the family history on both sides is particularly good. The father is a carpenter, a well-built, healthy, and sober man, aged 39, height 5 ft. 10 in., weight 15 st. He comes of a family of farmers and his eight brothers and two sisters are all alive and well. The mother, aged 33 years, is also from a healthy stock; her paternal grandmother is living, her father is in good health, her

mother died of puerperal fever, and her four brothers and two sisters are all healthy. The parents of the infant live in a clean and new tenement, with all reasonable comfort of their social position. This child is the third born, and during her pregnancy the mother was in specially good health. Labour began on the afternoon of October 18, the actual day which I had previously indicated as the probable date of delivery. The pains were slight and infrequent until after 8 o'clock p.m., when three quick and forcible pains completed the second stage spontaneously, the child being born immediately after a messenger had been sent to summon me. The child appeared to be a plump healthy boy, and he weighed 8 lb. The placenta was examined, and it showed no abnormality. On the following day (October 19), about thirteen hours after the birth, the nurse noticed that the child's face was of a dark bluish colour. This cyanosis soon passed off, but it recurred in the afternoon, five or six hours later. During the following night (October 19-20) these attacks came on more frequently and more violently, occurring almost every hour. Each attack began with three sharp screams, the eyes rolled, the hands became rigid with fingers clenched, and there was marked cyanosis of the face. Each seizure seemed to last about ten minutes, and it passed off gradually, leaving the child exhausted, but he had no proper sleep till October 22. They continued with about the same frequency until the evening of October 21.

When I saw the child on October 20, the report given of these attacks, with the marked cyanosis, suggested the possibility of cardiac malformation, but I could not detect any cardiac abnormality except the pulse-rate, which, by auscultation, I estimated as being about 200 per minute.

On the same day (October 20) the nurse drew my attention to the firmness of the thighs, and on having him undressed, I found the same condition over the buttocks and dorsal regions. The most notable feature was the half-frozen feeling or rubber-like consistency of the parts on pressure; there was no pitting, even on firm pressure; the skin could not be picked up from the underlying tissues, and, even when freely handled, there did not appear to be any pain. This firmness had been first noticed by the nurse on the afternoon of October 19, and it was then limited to the buttocks and the legs below the knees. Within seventy-two hours after birth, the induration was found over the dorsal and lumbar regions, also about the shoulders and face and jaws, with patches on the front of the abdomen and in the lateral costal regions. In these areas, the affection seemed to be in broad patches rather than limited to any special groups of muscles. The skin appeared to be normal in colour without any of the abnormal tints described by some writers.

I spoke of the case to Dr. Leonard Findlay, because of his special interest in the diseases of infancy; he saw the child twice with me, the first time being on October 21, and he agreed with me that the case was one of sclerema neonatorum. At his first visit, the child seemed to be quite unconscious, and the rectal temperature was 97° F.; there was external strabismus of the right eye, but this did not long remain present.

For the first week the child was extremely ill, and I could give very little prospect of recovery. For that reason I can give no continuous record of temperatures, as I was unwilling to have him disturbed to the extent necessary for taking the temperature in the rectum or axilla, particularly as such a procedure was not necessary for any purpose of treatment. There was not any noticeable degree of coldness of the skin, but this point must be considered in association with the fact that he was kept almost constantly in an extemporized incubator so as to maintain artificial heat.

During the first six days there was great difficulty in giving him any nourishment, this being due to the muscular rigidity. He was quite unable to suck, and had difficulty even in swallowing; our only method was to open the mouth and pour in about half a teaspoonful of fluid, which would be

swallowed slowly. After the sixth day the stiffness left the facial muscles and he became able to swallow with increasing ease.

While the onset of the disease was sharp—the change of appearance from that of a normal healthy new-born child to that of an infant apparently at the point of death occurring within seventy-two hours—the recovery from the disease was very gradual and without any well-defined stages. Dr. Findlay, at his second visit (November 2, 1912), could recognize a marked diminution in the degree of hardness as compared with that found by him twelve days previously; it was also noted then that in the mid-dorsal region there was an area of induration which seemed to be painful when handled.

The stiffness, particularly as it affected muscular action, was first seen to disappear after six days from the face and jaws. Thereafter, it gradually faded away from the thorax and abdomen, then from the dorsal region, then from the buttocks and shoulders, and lastly from the outer aspect of the thighs. This process of gradual resolution occupied fourteen to fifteen weeks, and on each thigh there was a firm patch easily to be felt for about three weeks after the other areas affected had regained their normal consistency.

For several months the child appeared to progress favourably, and the reports given to me were always satisfactory, but on a recent examination (February, 1915) it was obvious that his condition was not normal. While the facial expression was reasonably intelligent, there was a very poor attempt at speech. In sitting, he tended to lie over to the left side, and there was marked disability in the use of the left arm and hand. He could not walk nor even stand alone, but when supported under his arms, he tried to walk, throwing up each foot with an ataxic movement; the mother stated that these efforts to walk were gradually improving. There were no signs of rickets, and the condition in general was suggestive of some cerebellar lesion.

Of a second case I am able to give some account by the kindness of Dr. Findlay, who saw it at the out-patient dispensary of the Glasgow Royal Hospital for Sick Children. I was unable to see the child alive, but I had the opportunity to assist at the autopsy.

This child was male, illegitimate, born in miserable surroundings, and there was well-marked congenital syphilis; the mother stated that there had been a rash on the body when he was born; he had taken the breast freely, and there had been neither vomiting nor diarrhoea. He was supposed to be mature, but when first brought to the dispensary on his twelfth day (Oct. 9, 1913) his weight was only 4 lb. 10 oz.

Dr. Findlay's note of his examination makes mention that the body was small and emaciated, and there was a pemphigoid eruption over the body, especially on the buttocks, legs, and arms, while the soles and palms were also implicated; the rash was well-marked round the mouth and there was a patch on the left cheek; the mucous membrane of the lips was excoriated and there was an ulcer on the right anterior pillar of the fauces; the spleen was only just palpable; there was then no sign of sclerema. On the following day (October 10, 1913) he was again brought to the dispensary, and it was then noted that there was a well-marked and extensive rubber hardness which the mother had first noticed on the morning of the same day, so that she had difficulty in moving the limbs. This sclerematous stiffening affected the face and chest, and it was well marked on the buttocks, thighs, and calves, also about the deltoids, the arms, and extensor aspect of the forearms; there was no oedematous pitting, even on firm pressure. The child was jaundiced and obviously weaker than on the preceding day, but the cardiac sounds were comparatively good; he was unable to suck; the rectal temperature was 96° F. Neosalvarsan, grm. 0.075, was injected into the right gluteal muscles. The child died at 3 a.m. on the following day when fourteen days old.

When I assisted Dr. Findlay at the post-mortem examination (October 12)

the following conditions were found:—Icterus. Dried blebs of pemphigus, well marked on arms and hands, legs and feet, and on the lower abdomen. In the head of the pancreas a gumma about the size of a cherry. Left kidney showed an abnormally large suprarenal capsule; right kidney seemed normal. Liver was enlarged and of a dark greenish colour; gall bladder could not be emptied by pressure, on account of fibrotic thickening in the portal fissure. Brain was soft and oedematous, and the surface markings were not well defined; there were no signs of haemorrhage nor of thickening of the meninges.

Subsequent examination showed the presence of spirochaetes in the pancreatic gumma, also in the pancreas, liver, and adrenal capsules. Blood from the mother gave a positive reaction to the Wassermann test.

Sections of skin from the buttock were prepared by Dr. W. B. M. Martin, pathologist to the hospital, and also of normal skin from the abdomen of an infant of three months. Comparison of these sections and of photographs prepared for me by Dr. Martin does not show any increase of fibrous tissue in the case of sclerema as compared with the normal skin, but in the former there is a marked thickening of the rete Malpighii, and, perhaps, some abnormal increase and aggregation of the cells of the adipose tissue immediately underlying the dermis.

Morbid Anatomy.

On considering the pathological alterations found in the tissues as a result of sclerema, one finds some degree of unanimity in the more trustworthy descriptions. One important fact which seems to be well established consists in the absence of any constant visceral lesion. In the examination of such cases after death, there have been found at times various changes in the internal organs. The most notable of these have included pulmonary affections such as atelectasis, pneumonia, and, rarely, pleurisy; hyperaemia of the brain and its membranes, and also of the abdominal viscera, such as the spleen, liver, kidneys, and intestines; and haemorrhages under the pleural, pericardial, or cerebral membranes; while Henoch reports the occurrence of gastritis haemorrhagica in one of his cases. Although one or more of these gross lesions may have been found in different instances, the degree of severity being variable, there is none which occurs as a constant factor in the disease, and they are therefore to be considered as possible complications or secondary developments rather than as features which have any essential or causal relationship to the main condition.

The characteristic changes to be found in a well-marked case are those in the skin and the tissues underlying it. The results of Parrot's examinations, as quoted in brief summaries by Henoch and by Crocker, are as follows: Extreme atrophy with consolidation of the skin, including the rete Malpighii, of which the cells are scarcely visible, forming a compact mass with ill-defined contours. The horny layer is unchanged and only looks thicker by contrast with the thinned rete and corium. In the subcutaneous fat, the fibres of connective tissue are more numerous than usual and thicker, and the fat itself is considerably diminished; the fat cells are smaller and their nuclei can be distinctly seen. Most of the fat cells are, as in every form of atrophy, almost or entirely deprived of their fat; they are shrivelled into an oval shape and have a great

resemblance to the epidermic cells of the rete Malpighii. The blood-vessels, especially those of the papillae of the skin, are narrowed to such an extent that one cannot distinguish their lumen. Henoch adds that in certain cases observed in his wards, dissection of the skin had yielded similar results—drying up of the skin, with consolidation of its layers and atrophy of its tissues. Ballantyne, in a report of one examination, says that section of the skin and subcutaneous tissue gave the sensation of cutting bacon rind, and that the subcutaneous cellular tissue had a peculiar white glistening aspect, quite unlike the yellowish appearance of the subcutaneous fat in a normal infant. There was no serous fluid to be expressed and no macroscopic appearance of congestion. On microscopic examination, the outstanding feature of the sections was the presence of abundant brightly stained connective tissue, the fibres of which, increased in number and abnormally thickened, subdivided the adipose tissue into patches of varying size. The cells composing the connective tissue could be clearly differentiated, and there were also to be seen blood-vessels relatively large as compared with those in the papillae, each surrounded with leucocytes, and projecting into the groups of fat cells. In the adipose tissue, it was seen that none of the cells had their normal amount of oil, and some of them were devoid of fat; the nucleus in all was clearly visible, and in many a ring of protoplasm underlay the cell-wall. The papillae were not well marked and the cells of the rete Malpighii were ill defined. The horny layer appeared to be normal. Ballantyne, while recognizing the general correspondence of Parrot's description with his own, considers that the lesion is something more than cutaneous consolidation with atrophy of the tissue. In his opinion, the primary change is in the penetration of a capillary into the fat cells, the capillary being surrounded or accompanied by leucocytes; from this there arises an increased formation of fibrous tissue, and subdivision and atrophy of fat cells. Mensi, as I have already quoted, described the characteristics of one of his types to be atrophy of the skin with absence of the granular layer, the cells of the cutis being closely packed together, and there being dilatation of the vessels with haemorrhages into the skin. In the other type he describes atrophy of the skin, with abnormal development of fibrous tissue round the fat. He holds that the main feature of sclerema is in the alteration of the cutaneous fibrous tissue.

Finkelstein says that in this disease there may be hyperaemia of the muscles, with a small-celled infiltration alongside of each capillary.

In the report of a typical case given by Waterhouse there is a remarkable agreement with Ballantyne's description. He speaks of the unusual resistance to the knife on cutting, the alteration of the panniculus adiposus from the appearance of loose yellow greasy fat to that of a dead white layer, soft but compact, resembling dried sebum and closely adherent to the skin. He also notes the remarkable absence of normal fat even in the omentum and round the kidney. There was abnormal density of the connective tissue of the cutis vera, with fibres extending into the subcutaneous tissue, and the blood-vessels of the cutis vera had thickened walls.

It is to be recognized that the microscopic conditions found by different observers show some degree of variance. I would suggest that these variations may depend on the individual conditions of the cases described. In a case characterized by very severe symptoms passing rapidly into death, it might be that the end would come before the increase of the fibrous tissue had occurred. The microphotographs from Dr. Findlay's case show no appearance of abnormal fibrosis, but it is to be remembered that the child died within twenty hours of the signs of sclerema being first seen by the mother. If the symptoms were less violent, and the termination more gradual, time would be given for the development of fibrous tissue and for the atrophic changes in the adipose tissue.

From the various descriptions, one may conclude that the primary change consists in the infiltration with small cells of the true skin and subdermal layer and, possibly, of the rete Malpighii. As a secondary change, there would occur an increase in number and density of the connective-tissue fibres, with alteration in the shape and contents of the fat cells, and these latter features, when present, would be most prominent microscopically.

Aetiology.

To give some rational explanation of the cause of these morbid phenomena many theories have been propounded, ranging from the doctrine of maternal impression set forth by Uzembezius to that of septic intoxication suggested by Eustace Smith in 1898. Some of the earlier observers considered that the lesions were akin to erysipelas, or due to some inflammatory process, while others saw an analogy to phlegmasia alba dolens. Parrot, as has been mentioned earlier, considered that the induration was one of the features of athrepsia, due to faulty nutrition, overcrowding, and the like, and in this he was in agreement with Underwood's description of it as a hospital disease, at a time when the unsatisfactory state of the hospitals did much to cause disease. But debility, arising from the unfavourable circumstances which are often associated with sclerema, is not in itself sufficient to cause this peculiar affection. This is proved by the fact that the disease may occur in an infant otherwise healthy and free from the unhygienic influences of syphilis, poverty, immaturity, or squalor. Further, if these unfortunate conditions, which are so commonly encountered, or if any group of them, were the immediate cause of the ailment rather than predisposing influences only, then sclerema would be almost certainly a disease of common occurrence instead of being one of the rarities of medical practice.

It was suggested by Léger in 1823 that one of the main factors was the effect of cold in causing coagulation in the subcutaneous tissues of the new-born. Many years later, in 1881, Langer held a similar view, that the condition was essentially a physical change in the adipose tissue due to cold—an actual freezing or solidification of the fat, and this he based on his demonstration of

a marked difference between the fat of infants and that of adults. This observation was confirmed by Knöpfelmacher, and it was to the effect that the adipose tissue has in infancy more stearin and palmitin and less olein than in adult life. As a result of this excess of fatty acids, the difference being as 31 per cent. to 10 per cent., the fat of the new-born solidifies at 89.6° F., while that of adults solidifies below 32° F. This theory was accepted by Northrup (*Archives of Pediatrics*, 1890), and it has received a certain amount of support, but, to my mind, it is untenable. It is not consistent with the fact that the induration generally begins in the lumbar and gluteal regions, which are usually protected from cold, rather than beginning in exposed parts such as the face and extremities. It is not a probable cause of an induration which is found in irregular patches instead of being generalized over an area which might have been exposed to cold. It does not account for congenital cases. It does not explain the microscopic findings of increase of the fibrous tissue with actual atrophy of the fat cells, and the loss of some or all of their fat. Still further, if the essential lesion were a congelation of the adipose tissue, the persistence of the condition would be incompatible with the occurrence of pyrexia. In the case recorded by Waterhouse there were variable degrees of pyrexia, reaching as high as 105.6° F., but without any apparent difference in the indurated areas.

For these reasons, principally, I hold that the contention is unsound which would ascribe the cause of the disease to the results produced by cold on the adipose tissue.

Certain other suggestions by which the onset of the disease has been respectively attributed to *patency of the foramen ovale* or other disturbance of the circulatory system, to *pulmonary lesions*, to *shortness of the intestine* or other gastro-intestinal or hepatic affections, do not seem to call for much consideration, in view of the fact that typical cases of sclerema occur without the coincidence of any such conditions. Ballantyne, in his *Diseases of the Foetus*, devotes attention to various points as possible aetiological factors. He refers to the *incidence of sex* of the infants affected, to the *exact date* of the first symptoms, to the *state of health* of the infant or of one or both parents, to the *diet* of the child, and the *season of the year* when the disease is most likely to be found. It would serve no useful purpose to give a mere transcription of his statements, to which reference is easy, but his conclusions are that none of them has any direct bearing on the causation of the disease, and that, as predisposing causes, they are of importance only in so far as they contribute to the lowering of the vitality. He indicates his general agreement with the opinion that the primary cause is to be found in some *trophic disturbance of the nervous system*, and it is to be noted that Coats draws attention to the similarity of the lesion in sclerema with those found in certain tropho-neuroses.

This theory of nervous influence had been put forward first by Liberali in 1818, and, with various modifications, had been adopted by different writers,

including Angel Money (1889) and G. Somma (1892). The opinion of the last-named writer is quoted at some length by Ballantyne, and it may be summarized as follows: Somma accepts as proven the existence of thermogenetic, thermolytic, and thermotactic centres in the brain; from this he concludes that, given a congenital debility of the infant as a predisposing cause, there might follow chilling of the surface as a determining cause, and that from this centripetal stimulation of the thermotactic centres, there would follow the efferent impulses resulting in the local changes in the subcutaneous tissue. Various objections may be raised to the acceptance of this or any allied theory of causation. First, the existence of heat-regulating centres in the brain is chiefly hypothetical. Secondly, no cerebral lesions have been found as constant factors. Thirdly, congenital debility is not a necessary antecedent; it has been shown that the disease may occur in a child apparently in good health. Fourthly, chilling of the cutaneous surface is not an invariable concomitant; this is demonstrated by the facts that sclerema may occur in warm weather, and, still further, that the disease may be actually congenital, its manifestation having begun *in utero* without any exposure to cold. Fifthly, while the tropho-neurotic theory might reasonably give some explanation of the subcutaneous lesions, it does not so readily account for jaundice, subserous haemorrhages, or broncho-pneumonia, which are commonly found as complications.

The effects of internal glandular secretions have also been considered as possible causes of the disease, and reference may be made to the somewhat comparable condition found in myxoedema, where also there is an induration which does not pit on pressure. This aspect has been dealt with by Mensi (*op. cit.*), who concludes that there is no reason to ascribe sclerema to any change of the internal secretions. He suggests that possibly some variation of the thyroid secretion, either by increase or diminution of its efficiency, might act as a predisposing cause and might also assist to generate the toxic agent. It may here be stated that in the case which was under my care extract of thymus gland was used, according to Carpenter's suggestion, but it seemed to produce bad results, and after three weeks it was discontinued.

In the light of modern pathology, one is forced to consider the question of microbic effect in the production of such lesions as we find in sclerema, and it would seem that in this direction we are most likely to find a satisfactory explanation. This theory was put forward in this country by Eustace Smith in 1898, and it has been further elucidated by others, such as Schmidt, Jemma, and Comba, whose results would serve to show that there is no specific micro-organism, but that probably various organisms, either a simple or mixed infection of streptococci, staphylococci, or Friedländer's bacillus, may act as causal factors in the disease. A toxæmia of this kind would reasonably explain the multiplicity of conditions which have been described. It would account for the evidence during life of lowered vitality; for the pyrexia which is sometimes present or, by extreme prostration, for the subnormal temperature which may be one of the more striking signs of the disease; for the icterus mentioned by Henoch

as a very common symptom, which, in the absence of any hepatic lesion, may be of the ordinary type found in many healthy children, but which may also be due to some toxæmic destruction of the blood corpuscles.

Of the conditions found after death, septicaemia would also afford a rational solution. The microscopic findings of subcutaneous fibrosis, destruction of the fat, and increased leucocytosis besides the capillary blood-vessels are all suggestive of some toxic irritant. The other lesions which have been found as common, though not invariable complications—bronchitis, broncho-pneumonia, haemorrhages into the serous cavities, gastritis haemorrhagica quoted by Hensch, and the 'polyarthritis rheumatica' found in a case reported by Demme (1882)—cannot reasonably be explained as the results of anything but septicaemia.

In a contribution by Money, he records the occurrence of paralytic symptoms in cases which may have been sclerema, and he also suggests the theory of a tropho-neurosis. Acceptance of his report, however, does not necessarily militate against the microbic theory. It is well known that evidences of nerve injury may be found in some diseases which are undoubtedly of microbic origin. The post-diphtheritic paralysis due to the Klebs-Loeffler bacillus, the nervous phenomena due to the bacillus tetani, the general paralysis following the spirochaete of syphilis, and probably the symptoms of cases of epidemic poliomyelitis acuta are all instances of this type, although in the last named the recognition of a specific micro-organism has not yet been definitely established. Thus Money's observation of paralysis occurring in sclerema is not destructive of the microbic theory, but, by analogy, would tend to strengthen it.

Prognosis.

The prognosis in a case of sclerema must be always guarded, usually grave, but not invariably hopeless. It will in some measure depend on the extent of the local lesions and also on the presence or absence of complications. It will vary unfavourably or favourably according to the gravity of the signs exhibited, such as the record of the temperatures, the state of the heart, or other indications of prostration, the lower degree of temperature and the slower pulse giving the worse prognosis. It will be affected markedly by the general circumstances of the case, being better in the case of a mature child of sound constitution born into favourable surroundings than in that of a premature and weakly infant in adverse social and climatic conditions. It will also depend on the infant's personal degree of resistance to the actual materies morbi; in this respect, it is possible that hereditary tendency may have some bearing on the prognosis, as in the record by Money of three successive cases in one family which were possibly cases of sclerema accompanied by paralytic symptoms.

Treatment.

In dealing with a disease where there is lack of knowledge as to the cause, the first direction of therapeutic measures must be towards the treatment of symptoms. In sclerema the wide range of theories as to its cause and its essential features has led to a great variety of means of treatment, many of which have fallen into disuse. The necessity is obvious to place the child in the most favourable hygienic surroundings and to maintain its strength, as far as possible, by the administration of suitable nourishment. In my own case an extemporized incubator was used with satisfactory results. An ordinary clothes-basket was taken and pigeon-holes were cut in its lower segment, each one large enough to admit a lemonade bottle. Over a layer of bottles a bed was made, and the inside of the basket was lined so that the child was almost completely covered in. Each bottle in turn was slipped out, filled with hot water, and reinserted, so that the temperature was maintained at a fairly constant level. More elaborate methods to obtain the same result have been described by different writers.

As a remedial measure many have used warm baths from 90° to 99° F., with or without the addition of mustard or aromatic substances, the duration of each bath being from fifteen to twenty minutes. Underwood and some others recommended the use of vapour baths, while others again applied warm lotions to the skin.

Friction of the body and limbs has been considered serviceable, and also massage, with the inunction of olive oil, camphorated oil, or mercurial ointment, apparently with benefit. In my case I prescribed gentle rubbing with unguentum iodes, a composition having free iodine with an oleaginous base. This preparation has the advantage that, even with repeated applications, it does not cause hardening or vesication of the skin, and it was used daily for about four months. I am of opinion that it was beneficial, possibly from the alterative effect of the iodine, possibly by its promoting absorption of the induration, possibly too from the well-known germicidal action of iodine.

In the matter of internal medication, we find an extensive list of preparations which have been used and recommended. Diaphoretics, diuretics, emetics, aperients, and stimulants have all had their advocates, while digitalis, mercury, and cinchona have also had their supporters. Some have used drugs capable of subcutaneous administration because of the difficulty of swallowing, and the inhalation of oxygen has also been recommended. In the case which was under my care, the first indications were to combat the cardiac weakness. Whisky, in small quantities, was given by the mouth, 'Digalen' was used hypodermically, and on two occasions a subcutaneous injection of adrenalin chloride (1-1000) was also given.

For the general condition, extract of thymus gland, as suggested by Carpenter, was used for about three weeks. Of the 'tabloid' preparation of thymus gland, one grain daily was given at first, then one grain twice daily, and latterly two grains twice daily. After about three weeks the mother noticed that

the child became distinctly pallid for a while after each dose, and its use was therefore stopped.

If it should happen for me again to have a case of sclerema under my care, I would think it right to make a bacteriological examination of the blood, with the hope of discovering one or more causal organisms. Pending any such information and the possible preparation of an autogenous vaccine, I would think it reasonable to try the administration of a polyvalent vaccine, and to judge by the results as to the desirability of its repetition.

General Conclusions.

On general consideration of this strange disease, one is forced, by the limited opportunities for observation, to draw conclusions from the cases recorded by others, rather than from a wealth of personal experience. The main points which I have endeavoured to establish as being in accordance with our present knowledge are the following:

1. Sclerema neonatorum is to be recognized as a definite disease which may be found with or without the association of other recognizable morbid conditions.
2. It may vary considerably in degree as to the extent and severity of its manifestations, and also as to the gravity of the prognosis.
3. The name properly includes the so-called 'pseudo-sclerema', the differences between true and false sclerema being only those of degree.
4. While the disease is a rare one, it is probably of more common occurrence than the usually accepted ideas would suggest.
5. It is found at or shortly after birth, and usually in circumstances which are unfavourable to the welfare of the infant.
6. The most characteristic feature is the palpable subcutaneous induration, with which there may be associated abnormalities of temperature, most notably in the direction of its being subnormal.
7. Visceral changes may occur as complications, in the form of inflammations, haemorrhages, or serous exudations.
8. The description of an 'oedematous' type of sclerema is probably unwarranted, the oedema in such cases being a complication rather than an essential feature.
9. Microscopic examination of a well-marked case would show subcutaneous infiltration with small cells and increased fibrosis, with atrophy of the adipose tissue.
10. The origin of the disease is probably to be found in some microbial infection.
11. Treatment must be largely symptomatic, but also some form of treatment should be sought which would counteract the toxæmia.

BIBLIOGRAPHY.

A full bibliography is given in Ballantyne's *Diseases of the Foetus*, 1895, and special reference has been made for this monograph to the following publications:—

- Allbutt and Rolleston, *System of Medicine*, Lond., 1911, 2nd edit., ix. 38.
 Ballantyne, *Brit. Med. Journ.*, 1890, i. 403.
 Ballantyne's *Diseases of the Foetus*, Lond., 1895, ii.
 Bangs and Hardaway, *Diseases of the Skin*, 1898.
 Barrs, *Brit. Med. Journ.*, 1889, i. 994.
 Bouchut's *Diseases of Children* (trans. by Bird), 1885.
 Bristowe's *Theory and Practice of Medicine*, 7th edit., Lond., 1890.
 Carpenter, *Lancet*, Lond., 1906, ii. 158.
 Cautley's *Diseases of the New-born*, 1913.
 Coats's *Manual of Pathology*, 2nd edit., Lond., 1889.
 Duhring's *Diseases of the Skin*, 1895-97.
 Evanson and Maunsell, *Diseases of Children*, Lond., 1847.
 Finkelstein, *Lehrbuch der Säuglingskrankheiten*, 1908.
 Garrod, *Encyclopaedia Medica*, 1902, xi. 1.
 Goodhart's *Diseases of Children*, 6th edit., Lond., 1899.
 Gould and Pyle, *Cyclopaedia of Medicine and Surgery*, 1900.
 Henoch's *Lectures on Children's Diseases* (New Syd. Soc.), Lond., 1889.
 Jacobi's *Therapeutics of Infancy and Childhood*, Lond., 1896.
 Kennedy's *Management of Children*, 1825.
 Mackenzie, *Brit. Med. Journ.*, 1889, i. 1229.
 Mensi, *Zeitschr. für Kinderheilkunde*, 1911.
 Money's *Disease in Children*, Lond., 1887.
 Money, *Lancet*, Lond., 1888, ii. 811, and 1889, i. 526.
 Monro's *Manual of Medicine*, 3rd edit., 1911.
 Osler's *Practice of Medicine*, 7th edit., 1909.
 Parrot's *L'Athrepsie*, 1877.
 Pfaundler and Schlossmann, *Diseases of Children* (trans. by Shaw and La Fetra), 1908.
 Robinson's *Manual of Dermatology*, 1885.
 Simpson's *Obstetric Memoirs*, Edinb., 1855.
 Taylor and Wells, *Diseases of Children*, 1901.
 Walker's *Introduction to Dermatology*, 1902.
 Waterhouse, *Lancet*, Lond., 1906, ii. 1282.

THE EARLY DIAGNOSIS OF PULMONARY TUBERCULOSIS

By EDWARD G. GLOVER

Introductory.

WITH the recent quickening of medical interest in anti-tuberculosis measures, diagnosis of pulmonary tuberculosis in the so-called prebacillary stage has become the criterion of good practice, and sanatorium treatment, for good or ill, has received the approval of medical and legislative bodies.

The coincidental stimulation of lay opinion, however, has given rise to an unreasonable dread of the dangers of association with the phthisical subject or contact, with the result that sanatorium treatment—the only 'diagnostic' measure available to an employer of labour—frequently leads, even in the case of purely negative contacts, to a form of economic ostracism.

It is every whit as important, therefore, to diagnose and exclude from sanatorium treatment cases of recently healed or obsolete tuberculosis as it is to recognize quiescent disease or disease in the prebacillary stage, and, what is of greater moment to the practitioner, this diagnosis cannot, with a few exceptions, be made on the strength of clinical examination alone.

This last statement is borne out by the following theoretical considerations. If it can be proved that practically every adult has had at some time or other a tuberculous focus somewhere in his body; and, further, if it can be shown that a certain percentage of definite cases of pulmonary tuberculosis become spontaneously healed or abortive; and again, since it is agreed that a certain percentage of clinically advanced cases of tubercle do actually become arrested and afterwards healed, then it is not unreasonable to say that clinical examination of any adult at any time may indicate the presence of a lesion, varying in size from a few cubic centimetres to the greater part of a lobe, which lesion is giving rise to no symptoms and which is as a matter of fact at the time of examination a healed lesion.

Conclusive proof of the first proposition is afforded by the work, chiefly post mortem, of Harbitz (1), Hamburger (2), Lubarsch (3), and Naegeli (4), and the investigations, by means of specific tuberculin tests, of Escherich (5) and Hamburger (6) in Vienna, of Daske in Düsseldorf, and of Lapage (7).

Regarding the abortive type of case, Fishberg (8) states that this is extremely common; Neisser and Bräuning of the Breslau Clinic found 300 of 1,900 cases

of this variety; and the writer recently observed that of 100 cases admitted to a sanatorium without tubercle bacilli in the sputum, 20 gave a history of a positive bacillary find within a period of three months before admission, and 15 of these (75 per cent.) were entirely negative to subcutaneous tuberculin and to serum methods of examination on admission.

But quite apart from the theoretical possibility of confounding an obsolete lesion with an active focus, it is a fact that a large percentage of sanatorium cases have a very doubtful claim to be considered positive. To take a typical instance, in the King Edward VII Sanatorium (9) in spite of repeated and careful examination the following percentages of the total yearly admissions had no bacilli in the sputum:

1908-9: 28.6 per cent.; 1909-10: 25.6 per cent.; 1910-11: 26.2 per cent.; 1911-12: 24.7 per cent.; 1912-13: 31 per cent.; with an average of 27.2 per cent.; and in the annual reports of most tuberculosis institutions non-bacillary cases are usually included in Group I as prebacillary cases, to the gratifying inflation of the statistics of 'arrest'.

Now it has been pointed out by de Wesselow (10) that any lesion of the lung cannot, from anatomical reasons, be far from an air-passage, and it is reasonable therefore to expect that an active lesion would give rise to the presence of tubercle bacilli in the sputum after a very short interval or even before any clinical signs manifested themselves. It follows then that any case showing signs of involvement of the lung, say at an apex, but with a repeatedly negative sputum, calls for investigation by more delicate methods before a final diagnosis is arrived at.

The following investigation was carried out on a series of forty-seven cases certified as pulmonary tuberculosis and admitted to an open-air sanatorium for prolonged treatment. Each case was subjected to as exhaustive a series of tests as possible, with a view to finding in the first place in what percentage a diagnosis of active disease could be confirmed, and in the next what tests or series of tests give the most reliable results in diagnosis. They were chosen in every instance after a consideration of the sputum report on admission.

In spite, for example, of a reliable bacillary find prior to admission, the case was given the routine series of tests, if after admission no bacilli could be found or if there was no sputum. As animal inoculation was not available, a sputum was held to be negative when, after repeated investigation by the ordinary film method and after careful sedimentation examination, no bacilli could be found. The sedimentation method employed was that of Ellermann and Erlandsen (11), which has been proved by Herzfeld (12) to give the most satisfactory results, and which Radcliffe (13) has found to give a positive result in roughly 40 per cent. of otherwise negative sputa. Any case giving a negative result to sedimentation examination of the sputum was held to be a 'doubtful' case. The films were stained in every case by the Ziehl-Neelson method, the methods of Spengler and Much being discarded as giving no more accurate results.

In arranging a parallel series it was necessary for practical reasons to

exclude any test the diagnostic efficiency of which was in question or which could not be applied in the majority of cases. Thus the cutaneous tuberculin reaction and the precipitin reaction, which are admittedly of little value in diagnosis, were discarded; the albumin reaction of the sputum (14), a most questionable method of examination even if generally applicable (fourteen of these cases had no sputum, six had mere traces), was not investigated, and Arneth's (15) nuclear count was not made on the grounds that a method of examination claimed to be of essentially prognostic significance cannot *a priori* be of much value in early diagnosis. The tests finally applied to these cases were: The investigation of the complement fixation reaction, the estimation of the tuberculo-opsonic index, and the injection of test doses of subcutaneous tuberculin.

1. The technique of tuberculin-testing followed was that of Bandelier and Roepke: the patient, provided his temperature were normal, was kept at rest and given, at intervals of forty-eight hours, injections of albumose-free tuberculin, viz. 0.0002 c.c., 0.001 c.c., 0.005 c.c., and 0.01 c.c.; slight general reactions were ignored, but when a fairly marked febrile reaction occurred the exciting dose was repeated.

A focal reaction was held to have occurred where moist sounds could be heard for the first time at any part of the lungs, where there was an increase in previously noted moist sounds, or where definite dullness to percussion could be made out over a previously normal area.

Until recently subcutaneous tuberculin injection was the most delicate of all the available diagnostic methods, and it is generally admitted, after the work of Bandelier and Roepke (16), Otten (17), von Romberg (18), and Waltershöfer (19), that the focal reaction is definite evidence of active disease. The same, however, cannot be said either of general febrile constitutional reactions or of reactions at the site of injection (local reactions); Franz (20), Beck (21), and others have shown that a general reaction does not indicate active disease, and out of a series of seventy-nine negative cases investigated by the writer thirty-seven gave a general reaction to the first two doses, forty-seven reacted to later doses, and only fourteen gave no general reaction. The drawback to this test is in the first place that, even ignoring slight general reactions, reactions of such severity that the maximum dose (0.01 c.c.) cannot be given occur in the writer's experience in as many as 35 per cent. of cases; and in the next, that persistently febrile cases cannot be tested. At the same time a negative result to subcutaneous injection is of the very greatest value, and for this reason the test was carried out in all except febrile cases and cases with extensive physical signs.

2. The opsonic index technique followed was that of Wright (22), and every attempt was made to minimize the margin of error either in actual technical details or in counting methods. The pipettes, for instance, were standardized as to bore on a fine wire gauge, and the slides were renumbered before staining by some other member of the staff. Samples were taken from the case under

investigation before exercise, and one, six, and twenty-four hours afterwards. The exercise given was as heavy as the patient's interest would allow—usually one hour's heavy gardening—and was combined with deep breathing. Two normal control sera were put up in each batch and unity was taken as the mean of these separately counted controls.

In view of the writer's experience of the addition of debris to the emulsion—that whilst in some cases the exaggeration of the swing was most gratifying, in others the counts were erratic—all the sera were tested, with unmodified emulsions.

It is not proposed to enter into a defence of the accuracy of the opsonic index. That has been very thoroughly considered by Wright in his book, but it may be said that the accuracy of the index depends on the honesty and patience of the observer. He alone can say whether his results are of the slightest value, and the only satisfactory course to follow where the technique has been at all 'ragged' is to commence the estimation of a fresh index.

After a long series of experiments with known cases and known controls, the writer estimated his margin of error and established as his own standard that an index giving a swing of 0.27 or over was definite evidence of active disease: indices without any definite swing, but ranging either below 0.7 or above 1.3, were also held to be positive.

3. It is impossible here to describe in detail the technique of complement fixation as carried out in these cases by Dr. Radcliffe of the Midhurst Laboratory. A short reference to it is nevertheless necessary on account of the variations in the character of the antigen used by different observers, and also on account of such statements as were made so late in the day as December, 1914, by Lindsay (23), that 'complement fixation is still in the experimental stage', and that 'it would be premature to express any opinion upon its probable usefulness'.

It is admitted that until recently the results of investigation by this method have been very unsatisfactory, the best giving positive findings in roughly 50 per cent. of definitely positive cases. The results in bovine cases were just as unsatisfactory, except those of Hammer (24), which have not been confirmed. With the employment of new antigens, however, the results became more promising. Besredka (25), using an antigen grown in special egg-bouillon, obtains about 90 per cent. of positive findings in definite cases of tubercle, although the value of these observations is greatly impaired by the fact that syphilitic cases would also give positive results. Genaux claims to have got over this by extracting the fatty bodies from the antigen. Calmette and Massol (26), using as antigen a concentrated extract of washed tubercle bacilli with 1 per cent. Witte peptone, claim to have obtained 92.5 per cent. of positive results. Radcliffe (27), using as antigen a freshly prepared unsterilized emulsion in salt solution (0.85 per cent.) of living tubercle bacilli grown on glycerine-egg medium (the strength of the emulsion being 1:500), obtains a positive finding in 88.6 per cent. of positive cases.

Here is one of his latest returns :

No. of Cases.	Group (T. G.).	Complement Fixation.	
		+	-
96	I	87 = 90.6 %	9
281	II	256 = 91.1 %	25
118	III	96 = 81.3 %	22
495		439 88.6 %	56

McIntosh and Fildes (27), using practically the same antigen, get 76.7 per cent. positive cases in forty-three cases of phthisis: 80.7 per cent. positive in twenty-six cases of surgical tuberculosis, with the exception of tuberculous glands, where 37.5 per cent. only, out of sixteen cases, gave positive results.

In addition, Radcliffe has examined the serum of fifty-two healthy persons on 187 occasions with invariably a negative result; McIntosh and Fildes have examined eighty-seven controls from healthy and diseased (non-tuberculous) individuals, all being negative except three (two cases of leprosy and one of Addison's disease).

So far then as specificity is concerned, the figures of McIntosh, Fildes, and Radcliffe, even neglecting those of Besredka or of Inman, who used Besredka's antigen, are of themselves satisfactory evidence. But it is quite a legitimate point to raise, whether or not complete 'fixation' is definite evidence of an active process, as compared, say, with an arrested lesion.

McIntosh and Fildes answer this very definitely in the affirmative, and on the grounds that, since fixation does not occur in the case of the average person giving a positive cutaneous reaction to tuberculin, and since even in undoubted cases of gland-tuberculosis the percentage of 'fixations' is small, it is fair to claim that complete fixation in a suspected case of pulmonary disease means active tuberculosis. At the same time it is not unreasonable to suppose that, where there is an old history of substantial impairment of a lung, positive fixation may occur even for some years afterwards when the history and symptomatology do not point to a progressive lesion.

The reply to this argument would be, of course, that such disease, although seemingly healed, is really only quiescent—a view which has been held more generally since the work of von Behring (28). So far there are no figures obtainable on the point, nor can there be until the reaction has been as fully exploited as was the Wassermann reaction on the population of general hospitals.

The cases detailed below have been classified according to the result of the test injections of tuberculin, as follows:

I. Cases giving no focal reaction and no general reaction (or practically none).

II. Cases giving no focal reaction but a marked general reaction.

III. Cases giving a focal reaction.

To these have been added—

IV. Cases which, for various reasons, were not given test injections.

TABLE I. *Cases giving no Reaction.*

ABBREVIATIONS.—B. S. = breath sounds: P. N. = percussion note: V. R. or F. = vocal resonance or fremitus: E. and E. = Ellermann and Erlandsen's sedimentation method: A. F. = albumose-free tuberculin: L. R. = local reaction: G. R. = general reaction: T. B. (-) = no bacilli found: 0 = no sputum.

No.	T. B.	Focal Reaction.	Opsonic Index.	Complement Fixation.
1. Family history negative: vague general ill-health: no definite clinical signs in the chest: no sputum. Final test dose: 0.01 c.c. A. F.: slight local reaction: no sputum. Opsonic Index: 1.17, 1, 1.1, 0.99.	0	-	-	-
2. Family history negative: run down after influenza: cough developed: no sputum: impaired note rt. apex: increased V. R.: no adventitious sounds. Final test dose: 0.01 c.c. A. F.: slight local reaction: no sputum. Opsonic Index: 1.04, 0.97, 1, 1.12.	0	-	-	-
3. Family history negative: pleurisy 5 months before: 2 pints of effusion tapped (? pneumococcal): deficient movement rt. side: B. S. generally diminished: P. N. dull: increased V. R. generally: no adventitious sounds: sputum negative by 3 ordinary examinations: E. and E. (-). Final test dose: 0.01 c.c. A. F.: local reaction slight: very slight general reaction: sputum E. and E. (-). Opsonic Index: 0.91, 1, 0.97, 1.06.	-	-	-	-
4. Family history negative: 'progressive ill-health associated with gastric disturbances: history of slight cough: no definite clinical signs in lungs: well-marked presystolic murmur at mitral area: no sputum. Final test dose: 0.01 c.c. A. F.: no reaction at all: no sputum. Opsonic Index: 1.23, 1.11, 1.06, 1.23.	0	-	-	-
5. History of contact: some low fever: sent in on suspicion, no clinical signs in chest: no sputum. Final test dose: 0.01 c.c. A. F.: no reaction of any kind: no sputum. Opsonic Index: 1.09, 0.98, 0.99, 0.97.	0	-	-	-
6. Family history negative: history of pleurisy 3 months before: sputum at that time negative: P. N. dull lower half of rt. lung: loss of movement: B. S. diminished: no adventitious sounds: sputum negative by 2 ordinary examinations: E. and E. (-). Final test dose: 0.01 c.c. A. F.: no reaction of any kind: no sputum. Opsonic Index: 0.81, 0.87, 0.8, 0.94.	-	-	-	-
7. Family history doubtful: general ill-health for 6 months: chronic cough and sputum: persistent low fever: V. R. increased at rt. apex: no adventitious sounds: sputum E. and E. (-). Final test dose: 0.01 c.c. A. F.: no reaction of any kind: no sputum. Opsonic Index: 1.07, 1.11, 1.06, 1.0.	-	-	-	-
8. Family history negative: general ill-health: some chronic cough: no sputum: P. N. impaired rt. apex: B. S. harsh to 2nd rib: V. R. (+): no adventitious sounds: no sputum. Final test dose: 0.005 c.c. A. F.: no local reaction: no sputum. Opsonic Index: 1, 1.03, 1.2, 1.12.	0	-	-	-

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TABLE I (continued).

No.	T.B.	F.R.	O.I.	C.F.
9. Family history negative: some cough and sputum after a bad cold: P.N. impaired rt. apex: B.S. bronchial: no adventitious sounds: sputum negative to ordinary examination: E. and E. (-). Final test dose: 0.005 c.c. A.F.: some local reaction: sputum E. and E. (-). Opsonic Index: 0.98, 1.03, 0.98, 0.98.	-	-	-	-
10. Family history negative: some cough and spit: general ill-health for some months: no definite physical signs: sputum negative to 4 ordinary examinations: E. and E. (-). Final test dose: 0.005 c.c. A.F.: some local reaction: E. and E. (-). Opsonic Index: 0.9, 0.95, 0.9, 0.98.	-	-	-	-

TABLE II. Cases giving a General Reaction.

No.	T.B.	F.R.	O.I.	C.F.
11. Family history positive: 3 months before admission brought up some blood: slight persistent cough and sputum: P.N. impaired rt. apex: B.S. harsh: no adventitious sounds: sputum negative to 4 ordinary examinations: E. and E. (-). Final test dose: 0.01 c.c. A.F.: temp. 101° F.: malaise: L.R. (+): no sputum. Opsonic Index: 1.02, 1, 1.05, 1.09.	-	-	-	-
12. Family history negative: 6 months before admission gradually developed cough and spit: 4 months before brought up some blood: sputum examined then and T.B. said to be found: some retraction and limitation of movement of rt. side: P.N. dull at rt. apex: B.S. weak: V.R. and V.F. increased: (?) occasional click: some bronchophony: B.S. faint left side: sputum negative to 2 ordinary examinations: E. and E. (-). Final test dose: 0.01 c.c. A.F.: temp. 101° F.: malaise: L.R. (+): sputum E. and E. (-). Opsonic Index: 1.05, 1.16, 1.06, 1.14.	-	-	-	-
13. Family history positive: contact positive: history of chronic cough over 8 years: occasional traces of sputum said to be T.B. (-): associated chronic gastric trouble: no definite physical signs in chest: no sputum: cyclical menstrual temperature. Final test dose: 0.01 c.c. A.F.: temp. 102° F.: malaise: L.R. (+): no sputum. Opsonic Index: 1.13, 0.95, 0.95.	0	-	-	-
14. Family history positive: contact positive: cough and traces of sputum for over a year: T.B. said to be (-): associated anaemia: no definite clinical signs in chest: no sputum. Final test dose: 1.01 c.c. A.F.: temp. 103° F.: malaise(+ +): L.R. (+ +): no sputum. Opsonic Index: 0.85, 0.94, 0.88, 0.88.	0	-	-	-
15. Family history positive: always subject to catarrh: 6 weeks before admission 3j haemoptysis and occasional traces of blood in sputum: P.N. impaired at rt. apex: V.R. increased: no adventitious sounds: sputum negative to 4 ordinary examinations: E. and E. (-). Final test dose: 0.01 c.c. A.F.: temp. 100.8° F.: malaise marked: L.R. marked: sputum E. and E. (-). Opsonic Index: 0.71, 0.85, 0.72, 0.86.	-	-	-	-

TABLE II (*continued*).

No.	T.B.	F.R.	O.I.	C.F.
16. Family history negative: ill-health for 2 years: 2 months before admission dry cough for a few days: brought up 5j blood: no sputum since: P. N. impaired at rt. apex: V. R. and V. F. increased: no adventitious sounds: no sputum. Final test dose: 0.005 c.c. A. F.: temp. 101° F.: no sputum. Opsonic Index: 0.96, 1.06, 1.08, 0.98.	0	—	—	—
17. Family history positive: contact positive: sent for inspection: P. N. dull at rt. apex: V. R. increased: V. F. (+ +): some bronchophony: no adventitious sounds: sputum negative to 2 ordinary examinations: afterwards none. Final test dose: 0.005 c.c. A. F. (repeated): temp. 100.6° F.: malaise marked: L. R. (+ +): no sputum. Opsonic Index: 1.05, 1.1, 1.13, 1.06.	—	—	—	—
18. Family history doubtful: liable to catarrh: slight ill-health for some months: slight cough and sputum for over a year: sputum said to be T. B. (—): P. N. very slightly impaired at rt. apex: V. R. and V. F. increased: sputum E. and E. (—). Final test dose: 0.005 c.c. A. F.: temp. 103° F.: malaise marked: L. R. (+): some increase in cough: sputum E. and E. (—). Opsonic Index: 0.94, 0.89, 0.76, 0.89. NOTE:—This index was not satisfactory, but there was no opportunity for repetition.	—	—	—	—
19. Family history negative: some haemorrhage a year before: streaking of sputum (T. B. said to be absent): no physical signs in chest: sputum E. and E. (—): runs a persistent temperature unaltered by rest or exercise: tested carefully during a remission. Final test dose: 0.001 c.c. A. F.: temp. 102° F.: malaise: marked local reaction: no focal reaction. Opsonic Index: 0.98, 1.08, 0.98, 1.02.	—	—	—	—
20. Family history positive: contact positive: some chronic cough for 2 years with occasional sputum (T. B. said to be found 1 year before): P. N. slightly impaired at both apices: V. R. and V. F. (+) at both apices: no adventitious sounds: no sputum: temp. rather irregular. Final test dose: 0.005 c.c. A. F.: temp. 101.4° F.: malaise: some cough: local reaction marked: no focal reaction. Opsonic Index: 1, 1.13, 1.04, 1.	0	=	—	—
21. Family history negative: pleurisy (rt.) 11 years before and again 2 years before: some cough and sputum following last attack (T. B. said to be absent): general signs of thickened pleura over rt. side: no moist sounds: no sputum. Final test dose: 0.001 c.c. A. F.: temp. 100.4° F.: malaise marked: L. R. (+ + +): no focal reaction: same result to a repeat dose: no focal. Opsonic Index: 0.96, 0.92, 0.93, 0.91.	0	—	—	—
22. Family history negative: some cough and spit for a few months before: P. N. impaired rt. apex: B. S. faint to first interspace: no moist sounds: sputum negative to 2 ordinary examinations: E. and E. (—). Final test dose: 0.005 c.c. A. F.: temp. 102° F.: L. R. (+): no sputum. Opsonic Index: 1.05, 1.15, 1.04, 1.	—	—	—	—
23. Family history negative: always subject to colds: one month before admission some cough and spit: sputum examined (T. B. said to be found): P. N. dull at rt. apex: B. S. harsh and blowing: V. R. and V. F. (+ +): some bronchophony: no adventitious sounds: sputum negative to 5 ordinary examinations: E. and E. (—). Final test dose: 0.01 c.c. A. F.: temp. 102.8° F.: malaise marked: cough and sputum slightly increased: L. R. (+ +): no focal reaction: sputum E. and E. (—). Opsonic Index: 1.07, 1.24, 0.9, 1.02.	—	—	+	—

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TABLE II (continued).

No.	T.B.	F.R.	O.I.	C.F.
24. Family history negative: some cough and spit over a period of 18 months: some impairment of P. N. at left apex: no added sounds: sputum negative on 3 ordinary examinations: E. and E. (-). Final test dose: 0.01 c.c. A. F.: temp. 100.6° F.: malaise: local reaction (+): no focal reaction. Opsonic Index: 0.74, 1, 0.84, 1.14.	-	-	+	+
25. Family history positive: cough for over a year: no sputum: progressive loss of weight: on admission P. N. impaired to 3rd space: B. S. harsh: crepitations after cough over same area and all over rt. upper lobe and apex of rt. lower lobe behind: on left side in front crepitation to 3rd space and to level of 3rd spine behind. Patient not tested until 5 months after admission. Final test dose: 0.01 c.c. A. F.: L. R. (+): G. R. (+): temp. 100° F.: no focal reaction. Opsonic Index: 0.9, 0.78, 0.97, 1.3.	0	-	+	+

TABLE III. Cases giving a Focal Reaction.

No.	T.B.	F.R.	O.I.	C.F.
26. Family history negative: gradual ill-health: cough and spit for some months before admission: P. N. impaired at rt. apex: B. S. bronchial: no adventitious sounds: sputum negative to 3 ordinary examinations: E. and E. (-). Final test dose: 0.001 c.c. A. F.: temp. 103° F.: G. R. (+): L. R. (+): focal reaction at rt. apex: E. and E. (-). Opsonic Index: 1.12, 0.99, 1.1, 1.25.	-	+	+	+
27. Family history positive: history of cough for over 2 years: sputum for 6 months: P. N. dull rt. apex: B. S. bronchial, some crepitations above clavicle, also at apex of rt. lower lobe behind: sputum negative to 4 ordinary examinations: E. and E. (-). Final test dose: 0.005 c.c. A. F.: temp. 101.8° F.: G. R. (+): L. R. (+): focal reaction at both apices involved: E. and E. (-). Opsonic Index: 1.41, 1.35, 1.3, 1.45.	-	+	+	+
28. Family history negative: cough and spit for some months before admission: P. N. dull rt. apex to 2nd rib: B. S. bronchial: V. R. (+): some scattered clicks to 2nd rib, not increased on cough: sputum negative in 3 ordinary examinations. Final test dose: 0.01 c.c. A. F.: temp. 102° F.: G. R. (+): L. R. (+): focal reaction at rt. apex: sputum (E. and E.) T. B. (+). Opsonic Index: 0.81, 0.99, 1.09, 0.74.	- +	+	+	+
29. Family history negative: cough and spit following influenza: P. N. dull at rt. apex: B. S. harsh to 3rd rib: no adventitious sounds: sputum negative 3 times by ordinary method: E. and E. (-). Final test dose: 0.01 c.c. A. F.: temp. 100.2° F.: G. R. (+): L. R. (+): focal reaction rt. apex: sputum E. and E. (-). Opsonic Index: 1.03, 0.94, 0.34, 1.13.	-	+	+	+
30. Family history strongly positive: contact positive: influenza 3 months before: cough and sputum since: sputum said to be T. B. (+): deficient movement left side: supraclavicular retraction: B. S. deficient: some fine crepitations to 2nd left rib in front: V. R. and V. F. increased: no sputum. Final test dose: 0.005 c.c. A. F.: temp. 101° F.: malaise slight: cough increased: no sputum: focal reaction increased and extension of crepitations to 4th rib. Opsonic Index: 1.33, 1.26, 0.92, 0.76.	0	+	+	+

TABLE III (continued)

No.	T.B.	F.R.	O.I.	C.F.
31. Family history negative: 2 years before haemoptysis $\frac{1}{2}$ pint: sputum then said to be T.B. (-): 3 months before admission 1 pint haemoptysis: sputum again said to be negative: P.N. slightly impaired over left apex: some crepitations after cough to 3rd space in front and to 4th spine behind: sputum negative to 2 ordinary examinations: thereafter none. Final test dose: 0.01 c.c. A.F.: temp. 100.6° F.: malaise: marked L.R. (+): focal reaction in left upper lobe (increase in moisture). Opsonic Index: 0.65, 0.98, 0.87, 0.91.	-	+	-	+
32. Family history negative: chill 1 month before admission: haemorrhage $\frac{3}{4}$ iv: traces of sputum: T.B. said to be found: P.N. impaired rt. apex: V.R. and V.F. increased: some bronchophony (? adventitious sounds): sputum negative to ordinary examination: thereafter none. Final test dose: 0.001 c.c. A.F.: very marked malaise: L.R. (+ + +): increase in cough: no sputum: focal reaction at rt. apex (presence of crepitations). Opsonic Index: 0.91, 1.06, 0.91, 0.95.	-	+	-	+
33. Family history negative: pneumonia 1 year before: no cough or sputum on admission: P.N. impaired rt. apex: V.F. increased: some rhonchus: (?) some crepitations at rt. apex behind: (?) left apex. Final test dose: 0.005 c.c. A.F.: L.R. (-): G.R. (-): temp. normal: focal reaction both apices. Opsonic Index: 1, 1.09, 0.9, 1. NOTE:- Patient's temperature after exercise on opsonic test was 99.2° F., which is presumptive evidence of insufficient auto-inoculation.	0	+	-	-

TABLE IV. Cases not Tested.

No.	T.B.	O.I.	C.F.
34. Family history positive: contact positive: pleurisy rt. side one year before: dry cough ever since: no sputum: P.N. slightly impaired rt. apex: B.S. deficient rt. apex in front and behind: V.R. increased over same area: no adventitious sounds: patient ran a persistent irregular temp. at night up to 100.4° (rectal) which did not settle after 5 months' observation: not tested on that account. Opsonic Index: 1.04, 1.12, 0.93, 1.07. Provisional diagnosis: negative. After-history, 10 months later: still negative: no cough.	-	-	-
35. Family history negative: chronic ill-health for 2 years: dry cough for 1 year: gastro-intestinal disturbances, constipation, &c. for same period: no sputum: no physical signs in chest: runs a persistent low fever up to 100° F. (rectal): did not settle after 6 months' observation: not tested on that account. Opsonic Index: 1, 1, 0.96, 0.89. Provisional diagnosis: negative. After-history, 9 months later: still negative.	0	-	-
36. Family history negative: history of (?) pneumonia rt. side with (?) septicaemic symptoms: thought to be (?) miliary tuberculosis, (?) hysteria: P.N. impaired rt. apex: no adventitious sounds: sputum (T.B. -) on 3 examinations: temperature very irregular, independent of exercise: not tested on that account. Opsonic Index: 0.91, 1.03, 1.02, 0.99. Provisional diagnosis: negative.	-	-	-

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TABLE IV (*continued*).

	T. B.	O. I.	C. F.
37. Family history negative: pleurisy 4 years ago: 3j haemoptysis then: cough and traces of sputum for 2 years: 3iv haemoptysis 6 months before: P. N. impaired rt. apex: B. S. harsh and blowing: crepitations after cough to 3rd space in front (rt.) and over upper and apex of lower lobe behind: sputum negative to ordinary examination. Patient kept under observation without testing owing to extent of signs: 2 months later sputum examination gave T. B. (+). Opsonic Index: 0.86, 0.82, 1.04, 0.73.	+	+	+
38. Family history positive: contact positive: for some years past cough and spit every morning: 3 months before cough much increased: sputum increased: T. B. said to be found: P. N. dull rt. apex: B. S. harsh: V. R. and V. F. increased: (?) some crepitations on cough: sputum negative to 3 ordinary examinations: kept under observation without testing: 6 weeks later T. B. (+). Opsonic Index: 0.79, 0.71, 0.98, 0.76.	+	+	+
39. Family history positive: contact positive: 2 years before rt.-sided pleurisy: cough and occasional spit ever since: T. B. said to have been found 3 months before: P. N. dull rt. apex: B. S. markedly diminished over rt. front and behind from apex to base: some crepitations increased on cough opposite scapular process: no sputum on admission but kept under observation without tests for 2 months, when an isolated specimen gave T. B. (+). Opsonic Index: 1.11, 1.29, 1.01, 1.	+	+	+
40. Family history negative: some cough and spit for about 4 months back: T. B. said to be found: marked retraction of rt. apex: limitation of movement rt. side: P. N. dull to 3rd rib: B. S. generally diminished over upper lobe in front and behind: no adventitious sounds: sputum negative to 2 ordinary examinations: often absent: kept under observation without tests for 1 month: sputum by E. and E. gave T. B. (+). Opsonic Index: 1, 0.83, 1.0, 1.24.	+	+	-
41. Family history (?): pleurisy (rt.) 8 years before: chronic cough and occasional spit ever since: P. N. impaired to 3rd rib in front and to 5th spine behind: abundant crepitations over same area: P. N. impaired to 2nd rib on left side: also abundant crepitations: sputum negative to ordinary and E. and E. examination, but patient not tested and a subsequent E. and E. gave T. B. (+). Opsonic Index: 1.15, 0.99, 0.85, 1.01.	+	+	+
42. Family history positive: pleurisy (rt.) 3 months before: cough and sputum (T. B. said to be found): P. N. generally dull rt. side: marked flattening and restriction of movement: V. R. and V. F. increased crepitations after cough throughout: P. N. dull left apex: some crepitations: sputum E. and E. (-): not tested on account of extensive signs. Opsonic Index: 1.42, 1.29, 1.23, 1.03. Provisional diagnosis: positive.	-	+	+
43. Family history positive: haemorrhage 3 months before ($\frac{1}{2}$ pint): sputum gradually developed: P. N. dull rt. front: V. R. increased: crepitations all over front and to angle of rt. scapula behind: some crepitations at 1st left interspace: sputum E. and E. (-): not tested on account of extensive signs. Opsonic Index: 1.26, 1.19, 1.44, 1.05. Provisional diagnosis: positive.	-	+	+
44. Family history negative: influenza 6 months before: followed by cough and spit: on admission P. N. dull over left front: B. S. bronchial, some superficial crepitations all over front increased on cough: no sputum: temperature liable to sudden violent fluctuations. Opsonic Index (estimated on temperature alone, i.e. without exercise): 0.9, 0.93, 0.99, 0.86. One month later rt.-sided pleurisy with effusion ($1\frac{1}{2}$ pints), still no sputum: serous fluid gave positive fixation. Opsonic Index, re-estimated (this time on exercise): 1.17, 1.01, 0.9, 1.14.	0 0	- +	+

TABLE IV (continued).

	T. B.	O. I.	C. F.
45. Family history negative: some haemoptysis 4 months before admission and again at 2 months: some cough and sputum (T. B. said to be found before admission): some impairment at rt. apex and occasional crepitation at apex: some crepitations at level of 5th spine behind on rt. side and at 6th spine on left: no sputum: not tested on account of extensive signs. Opsonic Index: 1-16, 0-86, 1-12, 1-03. Provisional diagnosis: positive.	-	+	+
46. Re-admission of old case (3 years' standing): T. B. last found 1 year before: P. N. dull to 2nd rib rt.: some crepitations over rt. upper lobe slightly increased on cough: V. R. and V. F. increased: sputum: E. and E. examinations (-): not tested. Opsonic Index: 0-9, 1-44, 1-1, 1-05. Provisional diagnosis: quiescent disease not yet arrested.	-	+	-
47. Re-admission of old case (2½ years standing): T. B. last found 6 months before: P. N. dull rt. apex: B. S. deficient: occasional click at apex not increased on cough: some fine crepitations at left apex not increased on cough: no sputum or cough. Opsonic Index: 0-96, 1-01, 1-89, 0-93. Provisional diagnosis: arrested disease.	0	-	+

The following tables show in a more compact form the results of this investigation:

TABLE V. Cases tested with Tuberculin.

Result of Test Injection.	Cases.	Opsonic Index.		Complement Fixation.	
		+	-	+	-
No reaction	10	-	10	-	10
General reaction	15	3	12	2	13
Focal reaction	8	5	3	6	2

TABLE VI. Untested Cases.

Diagnosis.	Cases.	Opsonic Index.		Complement Fixation.	
		+	-	+	-
Negative	4	-	4	1	3
Positive	10	10	-	8	2

TABLE VII. All Cases.

Diagnosis.	Cases.	Opsonic Index.		Complement Fixation.	
		+	-	+	-
Negative	29	3	26	3	26
Positive	18	15	3	14	4

Although the number of cases fully investigated is small, it may yet serve to give some indication of the diagnostic value of serum methods.

It will be noticed that all of the cases giving completely negative results to test injections gave also negative results to serum examination. Of the fifteen cases giving no focal but a marked general reaction to tuberculin, three gave a positive index, and two of these three a positive complete fixation. One case, therefore (No. 23), was negative to all except opsonic methods, and it is

interesting to note that this case gave a history of T.B. in the sputum before admission. Of the two remaining cases giving a positive index and positive fixation, one (No. 24) had practically no physical signs, and the other (No. 25), although admitted with extensive signs, was not tested until five months after admission, when a definite degree of arrest might reasonably be presumed. Of the eight cases giving a focal reaction to tuberculin, five gave a positive index and six positive fixation.

It is important to note, however, that in only one of these cases (No. 33) were both serum methods negative, and there the auto-inoculation in the opsonic test was not above suspicion. Against this one case may be put the three cases giving a positive serum examination but no focal reaction.

In considering the value of serum reactions it must be remembered that in a large group of definitely positive cases, 10 per cent. may give for some reason or other a negative complement fixation, and this same fact may account for the negative fixations amongst those doubtful cases giving a focal reaction. With this fact in view the following conclusions may be stated concerning cases where the history or clinical examination points to involvement of the lung:

- (i) Positive complement fixation is strong presumptive evidence of active or quiescent disease.
- (ii) Positive complement fixation plus a positive opsonic index is definite evidence of active disease.
- (iii) A positive opsonic index is definite evidence of active or quiescent disease.
- (iv) Negative complement fixation is in nine cases out of ten evidence against active disease.
- (v) Negative complement fixation plus a negative opsonic index is almost definite evidence against active disease.
- (vi) A repeatedly negative opsonic index is definite evidence against active disease.

The bearing of these conclusions on the use of tuberculin test injections is evident.

Even if, in suitable cases, there be no danger from such injections, there follows from their use, in the bulk of cases, a very definite amount of discomfort and, more important still, in a large minority of cases, either they cannot be given or they cannot be fully carried through.

On the other hand, serum reactions—certainly complement fixation and almost invariably the opsonic index—can be carried out in every case.

It would seem justifiable, therefore, to conclude that where both serum reactions can be carried out, if necessary, on more than one occasion, there is no necessity to give test injections at all.

This conclusion is borne out still further by the result of serum reactions in cases not tested by injections. Of fourteen such cases, four were considered to be negative. Three of these could not be tested owing to fever, and the fourth was an old case presumably arrested (No. 47). All four gave a negative index,

and all except the arrested case negative fixation. Ten were considered to be positive, and none of these could be tested on account of the extent of clinical signs. All ten gave a positive index and eight of them positive fixation. Five of these later on developed T.B. in the sputum and a sixth a tuberculous pleurisy.

In addition, when the combined results of serum reactions and test injections are considered, they will be found to afford some indication of the diagnostic value of various degrees of clinical involvement of the chest.

In the following tables, clinical signs have, for sake of convenience, been divided into three categories: (1) where they were completely absent; (2) slight; where the apex of one lobe, say, was definitely impaired; (3) marked; where the clinical involvement corresponded with Groups II and III of the Turban-Gerhardt classification: i. e. extensive involvement of all of one lobe, or part involvement of two lobes, or involvement of three or more lobes.

TABLE VIII. *Clinical Signs in Tested Cases.*

Result of Test.	No Signs.	Slight Involvement.	Marked Involvement.	Total.
No reaction	4	4	2 (pleurisies)	10
General reaction	3	9	3	15
Focal reaction	—	2	6	8

TABLE IX. *Clinical Signs in Untested Cases.*

Diagnosis.	No Signs.	Slight Involvement.	Marked Involvement.	Total.
Negative	1	2	1 (arrested case)	4
Positive	—	1	9	10

TABLE X. *Clinical Signs in All Cases.*

Diagnosis.	No Signs.	Slight Involvement.	Marked Involvement.	Total.
Negative	8	15	6	29
Positive	—	3	15	18
Total	8	18	21	47

It will be seen that out of forty-seven doubtful cases investigated, only eight had no physical signs; four of these eight gave no reaction to tuberculin, three a general reaction only, and one (No. 35) was not tested owing to fever, but gave no serum reactions.

Eighteen cases showed a slight degree of clinical involvement, and of these four gave no reaction, nine a general reaction, two were not tested but were otherwise negative, and three alone were positive (two giving a clinical focal reaction and one T.B.). The degree of involvement was practically identical in all the negative cases, i. e. the percussion note was impaired or dull above one clavicle, the vocal resonance was increased, the breath sounds were harsh, or the

breath sounds were very faint and tubular. Some cases, however, had merely an alteration in resonance, whilst others gave some slight pectoriloquy or an impairment at another apex.

In none of the cases was there any moisture before or after cough, whereas in the three positive cases, two had some suspicion of moisture after coughing at an apex.

The cases showing marked impairment are even more interesting. Of eighteen cases with extensive signs, six alone were negative. Three of the six were old pleurisies with extensive impairment of lung surface, one was an old arrested case with large fibrotic tracts, one (No. 25) had not been tested until five months after admission and was probably originally positive, and the remaining case had some suspicion of moisture at the right apex.

The fifteen positive cases, on the other hand, gave in every instance evidence of moisture, usually increased on cough, at any rate over the most of one lobe and occasionally all over one side.

To sum up: of twenty-nine negative cases, twenty-six showed no signs of moisture before or after cough, whilst all of eighteen positive cases presented various degrees of moisture varying from a few clicks to abundant râles.

Before making any statement as to the value of early clinical signs in the light of these figures, it will be well to recall the standpoint of the purely clinical school, as instanced by followers of Krönig's (29) light percussion method. The careful mapping of Krönig's area, the noting of shortening of the area or of blurring of its inner margin or of relative dullness at both margins, are held to be sufficient evidence on which to demonstrate in any apex disease as small in area as a cherry. It is admitted by many that the method is very suitable for detecting old or healed lesions, but in spite of that, when a doubtful case comes to be considered, alterations in this area are considered to be strong evidence in favour of active disease.

The writer's series of cases is admittedly small, but it is at least typical of the run of doubtful cases in sanatorium practice, and in nineteen out of his twenty-nine negative cases a very definite alteration in Krönig's area was noted.

Indeed, in three only of the cases showing signs limited to one apex were positive results obtained.

But apart from the question of distinguishing obsolete from active lesions, there are other points in differential diagnosis to which reference must be made.

Four of these cases, for instance, which proved to be negative, gave a history of naso-pharyngeal catarrh and were in all probability instances of collapse induration of an apex following obstruction of the higher air passages.

Three negative cases had a history of chronic gastro-intestinal disturbances, and two of these showed impairment of an apex, one suffered from chlorosis, one from mitral stenosis (early), one from metrorrhagia, one from salpingitis, and six from chronic ill-health and slow fever with which was associated some cough and sputum and after examination an impairment of one apex.

It would seem then that, however common it may be to find early cases,

with T.B. in the sputum, having signs confined to one apex, it is not common to find active disease of one apex in cases where the sputum has been repeatedly negative.

Moreover, when such cases are established, it will be found almost invariably that there is some degree of moisture, however small, to be heard, before or after coughing, at the impaired area.

Summary.

The following conclusions are based on the results of this investigation :

(1) That about 62 per cent. of cases coming under observation as supposed early phthisis, but with no bacilli in the sputum, prove to be negative; nevertheless,

(2) that such negative cases may present clinical signs of impairment of percussion note, breath sounds and resonance at, at least, one apex; and

(3) that moist sounds in such cases are almost invariably absent: therefore

(4) it is not justifiable to diagnose active tuberculosis on the strength only of impairment of an apex;

(5) that active disease confined to one apex with a repeatedly negative sputum is not common;

(6) that where moist sounds are present, further investigation is needed to exclude or confirm the presence of active disease;

(7) that when this investigation takes the form of the complement fixation reaction along with the estimation of the opsonic index (if necessary, repeatedly) a final diagnosis can be made without recourse to test injections of tuberculin.

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REFERENCES.

1. Harbitz, *Untersuchung über die Häufigkeit der Tuberculose*, 1905.
2. Hamburger, *Wien. klin. Woch.*, 1907, xx, 1069.
3. Lubarsch, *Fortschr. der Med.*, Berlin, 1904, xxii.
4. Naegeli, *Virchow's Archiv f. path. Anat. u. Physiol.*, Berlin, 1900, clx, 426.
5. Escherich, *Wien. klin. Woch.*, 1907, xx.
6. Hamburger, *ibid.*, 1069.
7. Lapage, *Brit. Med. Journ.*, 1912, ii, 1375.
8. Fishberg, *Medical Record*, 1913, i, 921.
9. *King Edward VII Sanat. Annual Reports*.
10. Radcliffe and de Wesselow, *Proc. Roy. Soc. Med.*, Med. Sect., 1914, vii, 159.
11. Ellermann und Erlandsen, *Zeitschr. für Hygiene*, Leipz., 1908, lxi, 219.
12. Herzfeld, *ibid.*, 1910, lxvi, 336.
13. Radcliffe, *Midhurst Lab. Report*, 1910.

14. Glover, *Brit. Journ. of Tub.*, Lond., 1914, viii. 217.
15. Arneth, *Munch. med. Woch.*, 1905, lii. 542.
16. Bandelier und Roepke, *Lehrbuch d. spez. Diag.*, 1913.
17. Otten, *Med. Klin.*, Berlin, 1910, vi. 1089.
18. von Romberg, *Wiesb. Kongr. für inn. Med.*, 1910.
19. Waltershöfer, *Beiträge z. klin. Chir.*, Tübingen, Band xxi, Heft 2.
20. Franz, *Wien. klin. Woch.*, 1909, xxii. 991.
21. Beck, *Deutsche med. Woch.*, 1899, xxv. 137.
22. Wright, *Handbook of Technique of the Teat and Capillary Pipette*, Lond., 1912.
23. Lindsay, *Brit. Med. Journ.*, 1914, ii. 955.
24. Hammer, *Deutsche tierärztl. Woch.*, Hannover, 1912, xx. 593.
25. Besredka et Jupiele, *Ann. de l'Inst. Pasteur*, Paris, 1913, xxvii. 1009.
- Besredka et Manqukhine, *Compt. rend. de la Soc. de Biol.*, Paris, 1914, lxxvi. 180, and 1914, lxxvi. 197.
26. Calmette et Massol, *Ann. de l'Inst. Pasteur*, Paris, 1914, xxviii. 338.
27. McIntosh, Fildes, Radcliffe, *Lancet*, Lond., 1914, ii. 485.
28. von Behring, *Deutsche med. Woch.*, 1904, xxx. 193.
29. Krönig, *Deutsche Klin.*, Berlin, 1907, xi. 581, 617.